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Chief Editor Professor A. Wallgren

Karolinska Sjukhusets Barnklinik, Stockholm 60

Co-Editor Professor B. Vahlquist

Akademiska Sjukhuset, Uppsala

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CONTENTS

Vol 51 1962

Research Reports

Case Reports

Review Articles and Progress in Pediatrics

Proceedings of Pediatric Societies

Danish Pediatric Society

Supplements published in 1962

Announcements

Book Reviews

GENERAL INDEX

Author Index

Subject Index

Editorial

Until the beginning of this century medical authors from the small North European countries had to publish their articles either in their own language in a local journal or if the content of the paper was considered to be of some importance in a German, French or English periodical usually a German one During World War I publication in foreign journals became more and more difficult. These difficulties gave rise to discussion in Scandinavian pediatric circles of the possibility of editing a pediatric journal in an international language The economic risk was, however generally considered too great and the project was therefore turned down.

I Jundell, who was professor of pediatrics at Karolinska Institutet in Stockholm did not quite agree with this pessimistic view He believed that the financial difficulties might be overcome if pediatricians could be persuaded to make some sacrifices. After the war in 1919 Jundell engaged himself personally and successfully with the task of getting voluntary contributions from Swedish pediatricians to a "Guarantee Fund intended to cover for the first three years the annual cost of publishing a pediatric journal, provisionally called Acta Pædiatrica.

A group of leading pediatricians from the four North European countries had in the meantime made preparations to establish a Nordic Pediatri Association and to hold a congress in Copenhagen in 1919 After the congress Jundell presented the Scandinavian pediatricians with his plan to publish *Acta Pædiatrica* He informed them of the manner in which he had met the economic side of the business and he got their agreement to co-operate and to collaborate Professor O Medin in Stockholm was suggested to be the Editor of *Acta Pædiatrica* He had retired from the chair of pediatrics in 191_ At this time he was without doubt the best known Swedish pediatrician in international circles. He had also generously contributed to the "Guarantee Fund" When Medin did not accept the invitation Jundell was appointed Editor and the following Scandinavian pediatricians were elected "Redactores from Denmark S Monrad and O Bloch, from Finland O Lövegren, from Norway A. Johannesson and C. Looft and from Sweden A. Lichtenstein. After the second volume of *Acta* Th Frölich from Norway W Wernstedt from Sweden and A Ylppö from Finland were added in the group of "Redactores" and after the third volume on the following Dutch pediatricians entered the group. E Gorter J Haverschmidt and C de Lange In the years that have passed great changes have taken place in the group of Redactores Of those mentioned above only Wernstedt

and Ylppö remain the names of the present Redactores" are listed on page 2 of the cover of this issue of *Acta Pædiatrica*.

In the first number of *Acta Pædiatrica* which appeared on March 15 1921 Jundell indicated the program of *Acta* as follows. *Acta Pædiatrica* will serve as an organ for the scientific production within the field of pediatrics in the North European countries to appear abroad as a Scandinavian joint enterprise instead of being dispersed among the mass of papers in foreign periodicals. The articles should be published in English French or German, according to the decision of the author Each number of *Acta* should consist of about six printed sheets four numbers forming a volume The numbers should be published as soon as the articles could be printed The *Acta* was open to articles from foreign authors in all countries, if sufficient space could be found for them

The distribution and acceptance of *Acta Pædiatrica* as an international periodical was extended when the Transactions of the Second International Pediatric Congress in Stockholm 1930 were published as a volume of the *Acta* The temporary use of *Acta Pædiatrica* as a sort of organ for the International Pediatric Association continued for the next three congresses in London 1933 in Rome 1937 and in New York, 1947 Because the New York volume produced a substantial economic loss for *Acta Pædiatrica* although generously supported by the Congress Committee the volume not being bought by those attending of the congress as has been envisaged the publication of the transactions of future international pediatric congresses was stopped.

At the start is was decided that articles should be submitted to one of the Redactores of the author s country be read and critically scrutinized by him and then sent with his comments to the Editor This reasonable satisfactory and, for the Editor very helpful agreement did not function, however and soon the Editor had to take over the whole responsibility As in most European periodicals the 'Redactores became only an honorary group of people who are consulted in certain matters of publishing policy receive the annual reports of the Editor and the Treasurer in which way they have an opportunity to follow the development of *Acta Pædiatrica* and to make their remarks and recommendations. The editing of *Acta Pædiatrica* was for Jundell an honorary one man job and only seldom did he consult any experts about the value of submitted papers. The articles during his time were mostly written in German and were sometimes very long; Jundell accepted articles up to 50 printed pages, which at this time was the rule in similar German periodicals. Later on the submitted articles were irregularly but frequently sent to be evaluated by experts. In the fifties a panel of experts in different fields of fundamental and clinical pediatrics was formed constituting an Editorial Board providing the Editor with advice and recommendations regarding the submitted papers

During its first 39 volumes *Acta Pædiatrica* was published in four numbers which appeared at variable intervals, depending on the number of accepted papers and on the rapidity of processing and printing In 1948 this mode of publication was changed Each volume now con-

tained six numbers, which should appear at regular intervals during a calendar year Due to several circumstances (the reconstruction of the printing factory among others) the regularity was not satisfactory until 1956, but since then *Acta Paediatrica* has been regularly issued every second month, beginning with January

The supplements constitute a very valuable addition to the ordinary volumes of *Acta Paediatrica* They have always been distributed free of charge to current subscribers. The total number of supplements so far published is 129 Since 1955 summaries of the supplements have been printed in the current issue of *Acta Paediatrica* in order to bring the appearance of the supplement to the attention of the readers of *Acta*. While the supplements previously were published in German, a few of them in French, they are now solely in English

In looking into the articles of the first volumes one cannot refrain from commenting upon the standard of the translations, especially those in English and French. The translators were generally not medical people and at this time the knowledge of English and French among Scandinavian pediatricians was not what it should be. The translations were often met by critical comments by foreign readers An attempt to get English, French and German pediatricians familiar with Nordic languages to make the translations was not successful. Foreign colleagues however consented to correct the language in the translated paper and during the last ten years this has always been done In the thirties English articles became gradually more common and in some issues all articles were translated into English In 1960 the Board decided that all articles should be printed in English and that summaries of articles should only be in English. Previously the summaries had been translated into German, French and Spanish. The same difficulty of satisfactory translation mentioned above regarding the articles themselves also happened with the summaries. It was very difficult to get a correct translation of the summary into another international language and the publication and distribution of the issues often had been much retarded by the delay involved in translation. Abolishing translations of summaries was an improvement in the regularity of issuing *Acta*

An annual index has been published since 1951 A general index of the first 30 volumes of *Acta Paediatrica* was published in 1947 and is still available It has not yet been decided if there will be a new general index covering volumes 31–50

The typographical appearance of *Acta Paediatrica* has changed a great deal from the simple-looking mode of the first issues to the present design. From 1950 on the contents of the issue have been printed on the front page of the cover Double-column print was introduced in 1938 thus facilitating the reading of the articles

Jundell died in 1945 without having appointed a successor as Editor After his death it was not evident who formally owned *Acta Paediatrica* and who should be responsible for the debt due to accumulated losses during the war years The "Guarantee Fund was xhausted and there did not exist any regulations regarding the election of Editor or Executive Board An Acta Paediatrica Foundation" was now inaugurated which all Swedish pediatricians were invited to join by

paying a small fee. The primary task of the "Foundation" was to publish *Acta Pædiatrica* and to elect an Editor and members of the Executive Board. In 1946 regulations were proposed and accepted by the members of the "Foundation" The "Foundation" became the owner of the non-profit enterprise *Acta Pædiatrica* A. Lichtenstein was now elected Editor and A. Wallgren Co-Editor and after Lichtenstein's death in 1950 Wallgren was elected Editor and B Vahlquist Co-Editor and they still hold these positions The elections were submitted to the "Redactores" who approved them.

During World War II and the critical years that followed the armistice great difficulties arose in continuing the publication of *Acta Pædiatrica* because of the disappearance of European and American subscribers. In addition the prices of printing and paper were rapidly increasing and there were heavy restrictions in Sweden regarding the use of printing Somehow these difficulties were overcome and gradually *Acta Pædiatrica* began to rise again, the old subscribers returned and bought the back volumes of the *Acta* they had missed during the war and new subscribers arrived Thanks to the generosity of the Swedish State and the Swedish Society for Medical Research *Acta* could continue to appear From 1947 on the Danish Rask Örsted Fund has given support many times and for some years the Finnish Government has also supported *Acta* Very valuable financial contribution was received several times from the Nordic Pediatric Association in connection with its congresses In 1947 advertising was accepted by the Board as a means of lightening the financial burden.

The subscription rate of *Acta Pædiatrica* was at the inauguration 25 Swedish kronor (=5 dollars) per volume and remained the same until 1948 when it was increased to 45 kronor and in 1957 to 50 kronor The continued increase in the cost of printing and paper has made a further increase of the subscription rate necessary from the current volume on for subscribers overseas. With regard to the standard of the *Acta* the increase in the number of pages per volume and the many supplements, the price cannot be considered high, especially in comparison with other international pediatric journals

Our *Acta Pædiatrica* was the first journal to use this name Later on several new pediatric journals have been edited as *Acta Pædiatrica* the name however always being combined with the name of the country of origin of the *Acta* (*Acta Paediatrica Belgica Española Japonica Latina* etc.) In 1960 a Hungarian journal appeared as *Acta Paediatrica* published by the Hungarian Academy of Science in Budapest without the name being followed by "Hungarica" or any similar indication of where it is published. We feared that the consequences of their adopting the name of our journal could lead to misunderstandings in referring to articles published in our *Acta Pædiatrica* and the Hungarian *Acta* In the *Current Contents*" the Scandinavian *Acta* is printed a *Acta Pædiatrica*" and the Hungarian likewise a *Acta Paediatrica*" We would recommend that in referring to our *Acta Pædiatrica* the abbreviation "*Acta Pæ diat*" should be followed by (*Stockh*)" and the *Acta Paediatrica* published in Budapest as *Acta Paediat Acad Sci Hung*" a in the *Index Medicus*

Acta Pædiatrica has always been printed in the Office of Almqvist & Wiksell Book Printing Company Uppsala. There has always been excellent co-operation between the Company and the Editors of *Acta* and it is a great pleasure to extend to the Company the sincere appreciation of the present Editors and the expression of their deep gratitude for extremely good collaboration during the publication of the first 50 volumes of *Acta Pædiatrica*

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Department of Pediatrics and Institut of Hist logy Uni ersity of Göteborg Sweden and Psychiatric Clinic, Ulleråker Hospital University of Uppsala, Sweden

Familial Mongolism with Chromosomal Translocation also Observed in Normal Boy Member

by ORLA LEHMANN and HANS A. FORSSMAN

Penrose [11] demonstrated that the maternal age was lower for mothers with two or more mongolian children than for mothers with only one child with this condition. A series of papers published in *The Lancet* during 1960 contributed to the explanation why this was so In April of that year Polani *et al* [13] described a case of mongolism with only 46 chromosomes instead of the 47 supposed in 1959 to be typical of this disease It was in a study of three mongolian children borne by par ticularly young women that these authors found the 46 chromosomes in one case.

In August the same year Penrose *et al* [1*] published a paper about a family with two mongolian children, both with 46 chromosomes. A sister of these two children as well as their mother and mater nal grandmother had only 45 chromosomes. These three women with the 45 chromosomes were all phenotypically nor mal. The authors of those two articles concluded that the chromosomal aberration was due to a reciprocal translocation involving a No 15 and a No *1 chromosome (Denver nomenclature) The phenotypically normal members of the family with only 45 chromosomes and their mon golian offspring with 46 chromosomes had only 5 chromosomes of type 13–15 These persons also showed a chromosome resembling the ones in the 7th to 12th pairs and supernumerary to this group. The members of the family with only 45 chromosomes showed monosomy at the site of pair No 21 The authors concluded that the big unpairable chromosome of Type 7–12 was actually a combination of the main part of one chromosome from for instance pair No 15 and a chromosome of Type 21

Carter *et al* [ ] described a family with three mongolian children (two siblings and their cousin) all with 46 chromosomes and carriers of the translocation just described The mothers of these children were sisters, and they as well as the children s maternal grandmother were all carriers of the translocation and phenotypically normal The only other member of the family still alive a brother of the two mongolian siblings was normal genotypically as well as phenotypically

Buckton *et al* [1] observed the same phenomenon of translocation in three mongolian brothers and their phenotypi cally normal mother (A sister of the two brothers with no clinical signs of mongolism had died of leukemia.)

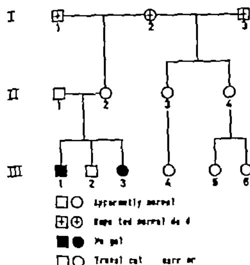


Fig. 1. The family tree.



Fig. 2. The boy III:2 at six years of age

Another type of presumed translocation within the small acrocentric chromosome group also associated with a chromosome count of 46 was described in mongolism by both Fraccaro *et al* [5] and Penrose *et al* [12] In both instances, the case in which they observed this phenomenon was the only one of mongolism in its family

The literature contains a number of further cases which are also presumably due to translocation but in which the chromosomes have not yet been studied Turpin & Lejeune [14] described a mother who gave birth to four unequivocally mongolian children and a fifth who was perhaps similarly afflicted. Jolly [8] reported two monozygotic twin sisters, one of whom gave birth to three mongolian children and the other to two Finally Carter (cited by Hanhart [6]) observed two monozygotic twin sisters each with one mongolian child.

Present Family

We have been studying the chromosome picture in familial mongolism for some time and hope to be able to publish a report on the entire investigation shortly Among these cases we found the family described in Fig. 1 All members of Generation I are now dead Judging by the available reports they were phenotypically normal. Cytologic studies were made in Cases 1 and 2 of Generation II. We found them phenotypically normal. According to information from No. 2, the same was true of her two half-sisters, Nos. 3 and 4 as well as their three children. In Generation III, No. 1 was a mongolian boy who died in 1934 No. 2 is the phenotypically normal boy seen in Fig. 2. No. 3 is a mongolian girl. The chromosomes of these two children were studied.

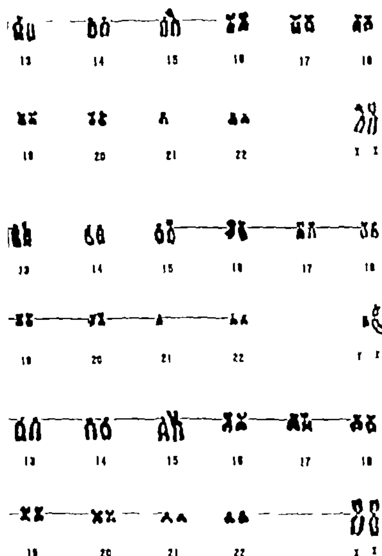


Fig. 3. Idiogram of translocation-carrying members of the family

Clinical Observations

II 2, the mother of the mongolian children, was phenotypically normal and looked healthy in every respect. She had ordinary hands with no four finger furrows and her ears were well shaped. Except for sideropenic anemia she had been quite healthy and had never been hospitalized. She had never had any unequivocal miscarriage but it was suspected that she had had an early miscarriage between sons III 1 and III 2.

III 1 born 1950. The diagnosis of mongolism was made at the Pediatric Department of the University of Göteborg where the boy was admitted at the age of 4

months and at his death in 1954 He died of bronchopneumonia. Autopsy revealed nothing wrong with his heart

III. born 1955 As seen from Fig * this boy looked quite normal. He was not deformed in any way: he had ordinary hands with no four finger furrows and his ears were well shaped. He was normally delivered weighing 3630 g after an uneventful pregnancy He walked at the age of 14 months and talked properly at 2 years of age. He was healthy until he was 4 years old, when he got bilateral otitis media Two weeks later he had a series of attacks of general convulsions. He was admitted to the Pediatric Department twice in 1959 EEG on several occasions showed epileptogenic activity and two months after the first fit, the pneumencephalogram showed slight dilatation of the left lateral ventricle Examination of the cerebrospinal fluid on the same occasion revealed nothing definitely abnormal. The boy is still under anti-epileptic medication, but it is more than a year since he had a fit. At the time of writing February 1961 he looks healthy and appears normally gifted, but he is keyed up and restless, as brain-injured children often are In 1959 an intelligence test of unspecified type was said to show an IQ of 82 He was under fairly heavy medication at the time the test was made His int llectual capacity seems to us better than indicated by this figure

III.3 born 1958. This girl suffers from unequivocal mongolism No heart defect was observed at th Pediatric Department of the University of Göteborg At the age of she was unable to speak at all, neither could she stand or walk. She was judged to have a DQ between 30 and 40

Cytologic Observations

We studied the chromosomes of leukocytes from circulating blood, using a slight modification of the technique described by Hungerford *et al* [7] We counted the chromosomes in 25 mitoses from each examined person and found the same number in more than 20 mitoses in each instance In no case was there reason to suspect chromosomal mosaicism in the blood cultures. Detailed analyses were *made of 4–8 mitoses in each of the cases.* The following observations were made.

- II.1 the phenotypically normal father had 46 chromosomes and a normal *idiogram.*
- II:2, the mother of the mongolian children, had 45 chromosomes and showed translocation of the type described in 1960 by Polani *et al.*, Penrose *et al* and others.
- III:2, the phenotypically normal boy had 45 chromosomes and showed the same translocation.
- III.3 *the mongolian girl*, had 46 chromosomes and showed the same translocation.

Observations on the satellited acrocentric chromosomes

As generally happens when we use blood cultures, we observed that the acrocentric satellited chromosomes tend t lie in close juxtaposition. The short chromatids in both the long and short chromosomes f this type be close together sometimes so close that they seem to be combined into one chromosome (Fig. 4*d* and), and sometimes connected to each other by bridges f faintly stained substance (Fig 4*f* and *g*). W have only occasionally observed these phenomena in cultures from skin and bone-marrow

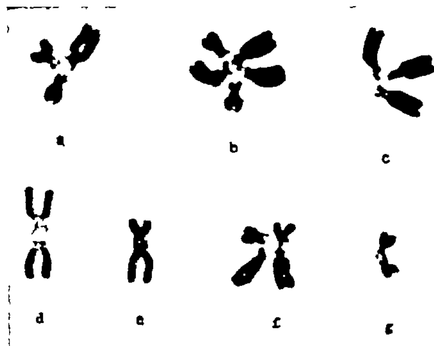


Fig. 4 a–c Acrocentric chromosomes around a faintly stained centre Some satellites are distinguishable d two long acrocentric chromosomes in close juxtaposition. one long and one short acrocentric chromosome close t each other resembling a translocation chromosome of type 15/*1 f two long acrocentric chromosomes, each of them joined to one short acrocentric chromosome by threads of pale substance, g two short acrocentric chromosomes, joined t each other through a mass of pale substance

Sometimes asteroid constellations appear in the mitoses; these constellations are built up entirely of acrocentric chromosomes, with their hort hromatids pointing towards a faintl stained centre where satellites can be distinguished (Fig 4a, b c). This centre is probably the nucleolus. The same condi tion is seen in other organisms where the 'stalks of the satellites make up the nu cleolus. Levan [9] found a simila arrangement of chromosomes in a star around the nucleolus in *Dipcad serot um* Levan & Hsu [10] also found nucleolar remnant t tached to a sat llited human hromosome

Comments

It may be that the nucleolar substance could become abnormally resistant to nuc leolar breakdown in some cases and the satellited chromosomes therefore ha d fficulty in breaking off their bonds of nucleolar substance This would prevent a chiasma from forming during meiosis and the chromo somes would keep together unpaired but connected to each other and moving to one pole If this phenomenon happens to the chromosomes No 1 in a gamet which is fertilized this leads to mongolian trisomy This has alread been suggested by Polani *et al* [13] and others

The fact that the satellited chromosomes are arranged around the nucleolus may lso explain the translocation phenomenon between them. Breakage of the nucleolar or ganizers and close association between the sat llited ends of the chromatids might f vor the occurrence of reciprocal translocation The fact that several translocations between sat llited acrocentric chromosomes have already been observed support this theory

Turpin & Lejeune [15] gave a survey of the chromosome translocations hitherto found in man.

Discussion and Summary

It is the unanimous experience that hereditary mongolism with translocation of Type 15/21 is always conducted by phenotypically normal women. So far it has never been possible to track down the translocation phenomenon to its origin, as it has been found in the oldest living generation of all the families studied. If we list the offspring of the translocation carrying, phenotypically normal women covered by the chromosome studies referred to here we find 8 mongolian children (7 males, 1 female), 4 phenotypically normal female carriers of the translocation, and one genotypically and phenotypically normal male (This does not take into account the non mongolian children who died early and were not studied cytologically.)

The female carriers of the translocation in our family gave birth to two mongolian children and also to a phenotypically normal boy who proved to be a carrier of the translocation. This is the first indication so far found in families with translocation of Type 15/21 that a man may cause mongolism in his offspring genetically. It may be that these men are sterile but it seems hardly likely. No male carrier of the translocation was observed in the other families studied through three generations, but this is probably due to a mere chance and to the fact that only a few translocation families have been examined so far.

The male translocation carrier in our family suffers from convulsions. However there is every reason to presume that this symptom is a sequel of a cerebral infection and has no connection whatsoever with the chromosomal abnormality.

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(O.L.) Barnsjukhuset
Goteborg
Sweden

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From the University Clinic of Paediatrics, Rigshospitalet Copenhagen

Cranial Circumference of Premature Children*

by LILLI JUSTESEN

Because there is only a little published information regarding the cranial cir cumference at birth of premature infants measurements have been performed in infants in order to elucidate this question

The largest circular fronto-occipital cir cumference has been measured at the point where the circular fronto-occipital circum ference is greatest All the measurements were made with the same tape measure. All measurements were on healthy infants, since infants, for instance those with cyanosis, convulsions, harelip, cleft palate and mongo lism were excluded, as were infants of dia betic mothers. In addition the cranial cir cumference of a number of older children admitted t the Paediatric Department of Rigshospitalet was measured, and in this survey only those cases showing disturban ces f growth or mental function (including oligophrenia) were omitted

Fig 1 shows the mean cranial circum ference at birth in relation to birth weight divided into increments of 100 g The highest and lowest value measured in each group is also shown The head cir cumference f the boys was slightly greater than that of girls.

In order t determine the increase of cranial circumference of premature chil dren a number of children with birth weights up to 2500 g have been observed serially (Fig 2) The birth weight of these children was distributed as follows: 1000 g, 2 children 1060–1500 g, 0· 1550–2000 g, 30· 2050–2500 g, 31

By comparing Fig 1 and * it may be seen that by the time premature babies achieve the level of normal birth weight their cranial circumference is somewhat greater than that of full term newborn babies Despite this it appears that the cranial circumference of premature chil dren is below average throughout childhood on the basis of age (Fig 3 and 4) Although the number of children examined is too limited to establish normal values the results seem to indicate that it is necessary to take the birth weight into consideration when assessing a child cranial circum ference There is no apparent difference in the cranial circumference during child hood between infants who weighed 2000 g t birth and those between 2000–2500 g Because of th small numbers in the lower weight groups similar comparisons are not possible.

Summary

When a premature child has reached th weight of a full term newborn its head circumference is slightly greater than

* This investigation as supported by PHS research grant B-406 from the National In stitut of Neurological Diseases and Blindness, U S Public Health Service

that of a mature newborn. It is shown that up to the age of 12 years the head circumference is on an average ½–1½ cm smaller in infants with a birth weight of 2500 g and less than in those with a birth weight over 2500 g. This applies to both boys and girls.

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Marielystvej 24
Copenhagen
Denmark

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From the Departments of Paediatrics and Child Psychiatry at Kronprinsessan Lovisas barnsjukhus, Stockholm

Suicidal Attempts in Adolescence and Childhood

by C. G BERGSTRAND and U OTTO

Only a relatively small number of investigations concerning the incidence of suicides and suicidal attempts in childhood and adolescence have been published. There are also good reasons for assuming that the figures vary from country to country and that the results are not universally valid, since the frequency of suicides in relation to the total population shows important variations in different countries [1 5 9 13 15].

The purpose of the present investigation was to study the frequency of suicides and suicidal attempts in Swedish children and adolescents. It was further considered to be of interest to collect data on the social background of the patients, the method of and the reasons for the attempted suicide In this survey no attempt has been made to penetrate in detail the psychological and psychiatric problems underlying suicidal attempts made by children and adolescents.

Material

For the period 1955 through 1959 case notes on patients under 21 years of age who had been treated because of suicidal attempts were requested from all hospitals in Sweden The only exceptions were special lnics to which patients of this type are usually not admitted. Of 4 1 relevant hospitals and advisory instit tions 463 (99%) furnished information

From the majority of the hospitals all dat available in the case notes were btained. A few hospitals were only ble to furnish information on the number of patients, their sex, ge and the method of the suicidal attempt. Because several patients had first been treated in one hospital, and then referred to another the material was checked with a view to excluding, as far as possible overlapping in the registration f the cases. The total material thus screened consisted of 1727 patients from all parts f the country

The number of suicides wa derived from the fficial statistics [15].

Results

Of the 1727 patients 351 (20%) were boys, and 1376 (80%) were girls.

The *age distribution* is shown in Fig 1 The youngest patient was 10 years old.

Fig * shows the *annual rate* of suicidal attempts for the relevant period.

The *seasonal variations* can be seen in Fig 3 The highest frequency was observed for November (147) and the lowest for June (9*) and July (81)

In 512 patients information was obtained of the *t me of the day* t which the attempts were made The majority oc curred late in the afternoon or during the

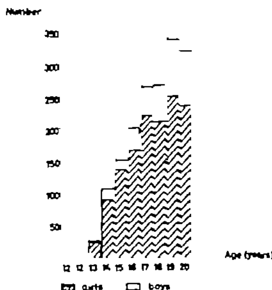
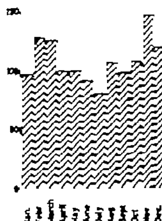


Fig. 1. Distribution by age and sex of children and adolescents having attempted suicide.


Fig. 3. Distribution by months of suicidal attempts made by adolescents and children.

night before 12 p.m. Only 6 % of the attempts were made in the morning.

For various reasons it was not possible to make a reliable comparison between

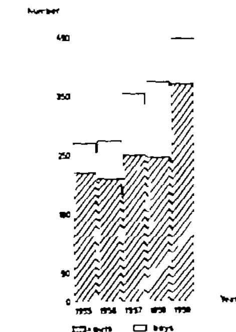


Fig. 2. Distribution by sex and year of children and adolescents who attempted suicide.

the incidence in urban and in rural districts, but 38 % of the patients (6.0) resided *in the three largest cities: Stockholm*, Göteborg and Malmö, which represent 10 % of the total Swedish population.

Reasonably reliable information on the *social background* and the *school conditions* was obtained in approximately 1000 cases (Table 1). The majority (83 %) of the patients belonged to the low income group (Social group III). If the sizes of the income groups in Sweden are compared it becomes evident that the low income group is over represented. Most of the patients (70 %) were attending elementary schools (folkskolor) or had finished at such schools. 7 % were attending the upper forms (grades) of secondary schools (gymnasium) or had passed the entrance examination to the university and the remainder were attending or had finished at other types of secondary schools (flickskolor, realskolor, tekniska skolor, etc.).

Seventy-eight patients (5) were of foreign origin, chiefly refugee youths, who arrived in Sweden during and after the Second World War.

TABLE 1 *Distribution by social groups of suicidal attempts mad by adolescents and children in relation to corresponding distribution of voters participat ng in the 1953 elec tion to the Second Chamber of the Riksdag*

Social group	Suicidal attempt		Voters
	Number	%	%
I	95	9.9	5.4
II	73	7.6	39.6
III	794	82.5	55.0

Adequate information on the family environment was obtained in 9?7 cases (Table 2) With few exceptions the home environment was considered noteworthy in one or several respects. In only 4_ cases (4 %) were the family conditions considered entirely normal. Alcoholism was recorded in one or both parents in 15 % and in 28 % the parents were mentally ill or revealed neurotic disorders to such a degree that the physician in charge of the case re corded them A broken home (because of divorce death of one parent unmarried mother etc.) was reported in nearly half of the cases (44 %)

The reason for the suicidal attempt was indicated in nearly 1300 cases (Table 3) The preponderant immediate reason was love problems (30) followed by family problems (_5 %) Girls were in the majority in these two groups Boys constituted a relatively large part of the group having

TABLE *Home and e vironmental conditions*

Nature of environmental conditions	Number	
N noteworthy factor	43	4.6
Alcoholic parent( )	135	14.6
Noteworthy mental conditions of parents	256	27.6
Incomplete home environment	407	43.9
Other noteworthy environmental conditions	87	9.4

TABLE 3 *Reasons for suicidal attempts*

Reasons	Sex		Total	
	♂	♀		
	Number	Number	Number	%
Love problems	56	336	39	30.3
Home and parental problems	41	280	3_1	24.8
School problems	12	80	62	4 8
Mental illness	66	109	175	13.8
Military service	17	—	17	1.3
Pregnancy	—	34	34	2.6
Other	64	229	293	22.6

TABLE 4. *Methods of suicidal attempts*

	Sex		Total	
Method of suicidal attempt	♂	♀	Number	[illegible]
Narcotic drugs	[illegible]	1232	1601	86.9
Hanging and strangulation	4	17	41	
Shooting	4	1	5	
Gas poisoning	14	19	3	
Leaping from height	8	10	18	
Throwing self before vehicle	1	6	7	12.1
Drowning	5	13	18	
Cutting self	15	51	64	
Swallowing sharp object	6	1	7	
Other methods	5	27	3	

school problems and dominated the group suffering from mental illness (boys 10 %, girls: 8 %). The latter group refers to all patients who according to the examining physician, had shown signs of psychosis or serious character disorders or who were definitely neurotic. Of 30 boys doing their military service at the time of the attempt 17 found the service so trying that they indicated it to be the decisive cause of their act. Extramarital pregnancy was declared to be the immediate cause in 34 girls.

The method of the suicidal attempt was recorded in all patients. As can be seen from Table 4 the most common method was ingestion of various kinds of drugs most of which belonged to the barbiturate group. Other methods constituted a rather small proportion (13 of the total number). Among the boys a relatively large group employed more violent methods, such as hanging strangulation the use of firearms or of cutting objects.

Table 5 shows that 60 % of the patients underwent psychiatric examination following immediate treatment. The impression emerged that these examinations were performed not so much because of the degree of severity of the case itself but rather because of the availability of expert psychiatric consultants within a reasonable distance. Of the 1960 cases where the measures taken were recorded less than one-third (30 %) were referred to psychiatric clinics or mental hospitals. Slightly over two-thirds (70) were returned to their homes immediately but many of these patients remained under psychiatric observation. There was a

TABLE 5. *Measures following immediate treatment*

	Sex		Total	
Measure	♂	♀	Number	
Psychiatric consultation	257	941	1198	63.4
Return to home	83	811	894	70.4
Referred to psychiatric clinic or mental hospital	109	[illegible]	[illegible]	[illegible]

TABLE 6 *Frequency of recurrent suicidal attempts*

Number of recurrences	Sex ♂	♀	Total Number	%
1	48	123	171	8.9
> 1	[illegible]	71	98	5.[illegible]
Total	73	194	[illegible]69	15.[illegible]

marked difference between the sexes, namely 31% of the boys and only 20% of the girls were considered to need continued psychiatric care

Table 6 indicates the *frequency of recurrence* Approximately every 10th patient had made an earlier attempt and every 20th had made several such attempts. These figures should however be considered uncertain, and in any case are definitely minimum figures. Repeated attempts were more common in boys.

The number of suicides committed in the age group 0–24 years during the period 1955–1958 is indicated in Table 7

Discussion

For several reasons the present survey cannot pretend to disclose the exact number of suicidal attempts made in Sweden by children and adolescents, an undertaking which appears to be impracticable Nonetheless the data should be regarded as representative even though some uncertain factors must be taken into account

Sometimes other persons in the patient environment conceal the fact that a suicidal attempt has been made and the event may have the appearance of an accident to the physician This may be assumed to occur more often in the upper than in the lower strata of society [10] It should further be kept in mind as is clearly apparent from the present material that a large proportion of those who attempt suicide in the age groups under discussion are adolescents who took tablets at bedtime. It is probable that many cases of this type where spontaneous awakening occurs the following morning are not interpreted by the environment as suicidal attempts, and the person concerned is not brought to a hospital and does not even consult a physician. Another source of error may be that the patient although he is brought to a hospital is

TABLE 7 *Number of suicides committed in Sweden 1955–1958 by age groups 0–24 years according to the official Mortality Statistics*

Year / Age	1955 ♂	♀	Tot.	1956 ♂	♀	Tot.	1957 ♂	♀	Tot.	1958 ♂	♀	Tot
< 15	2	1	3	1	—	1	1	—	1	—	—	—
15–19	11	2	13	13	8	21	14	7	21	10	8	18
20–24	24	11	35	39	14	53	34	19	53	15	11	26

never admitted or registered but sent home directly because his somatic symptoms are insignificant For these reasons the figure indicating the frequency of suicidal attempts should be considered as a minimum rate this is probably also true of the official data published by other countries on the incidence of suicides committed in their national territories

Further it is very difficult especially in a survey of this character where a thorough psychiatric analysis is lacking in many cases to always determine whether *a suicidal attempt in the strict sense of the* word has really been made Thus the borderline between an accidental over-consumption of sedatives and a planned suicidal attempt is surely indistinct in many instances.

In thi connection it should also be noted how seldom extramarital pregnancy was indicated as the reason for a suicidal attempt It is possible that some of the patients in this category were registered as having attempted abortion. It is also presumable that certain attempted abortions were registered as suicidal attempts since the patient may rather explain her taking of tablets a such an attempt than as an intended abortion, which is regarded a a criminal act

Thu one i faced altogether by rather delicate problems of definition In the present survey all cases interpreted a suicidal attempt by the physician treating the patient have been accepted as such

Boys constitute about one-fifth of the total material whereas they are twice as numerous a girls when t comes to actual suicides (Table 7). This confirms observations by others [1 3 9].

As can be expected, the number of suicidal attempts increases with age A steep rise can be observed especially related to puberty which too is in conformity with earlier observations [4]

During the period 1955–1959 the number of suicidal attempts increased considerably in both boys and girls but the question is whether this increase is real. It should be noted that the age groups studied coincide in the main with the large number of children born during the first five years of the 1940 s and therefore the relative frequency has not increased as *sharply as the figures seem to indicate*

When reviewing the official Swedish Mortality Statistics for the period 1925–1950 Hartelius found that in the population over 15 years of age the absolute number of suicides had increased while the incidence had decreased relative to the entire population. The decrease wa due to a decline in the number of male suicides whereas the women s share had actually increased. A further study of the data collected by Hartelius concerning the age group under 20 years shows that the male preponderance is less marked in thi group than in the adult population and that no increase in the frequency of suicides can be found, when comparing the groups born 1925–1937 with those born 1938–1950 While behaviour disturbances such as alcoholism and criminal offences have a tendency to make their appearance at younger and younger ages no such tendency can be discovered in respect to suicides. The present investigation seem however to indicate that at least the suicidal attempts have increased in the younger age groups during later years.

Some fluctuation in the incidence of suicidal attempts was observed during the

different months of the year in this series. The lowest number were during June and July while the highest were in November followed by February and March. Hartelius noted a peak in May for all ages, and the lowest frequency during the darkest months, namely November through February while Ettlinger & Flordh, who studied 500 suicidal attempts made by adults in Stockholm found a comparatively even distribution during the year with a certain rise in the spring and the autumn. There are reports from America of peaks in the statistics of suicidal attempts among children and adolescents during spring and early summer [10]. The stress of the school work during that period was given *inter alia* as an explanation. This would seem to be an unimportant factor in the present series because 70 % were adolescents who had finished school. It is still unclear why Swedish children and adolescents are more inclined to make suicidal attempts during the darker half year.

Sainsbury has studied the frequency of suicides in different districts of London, and found that it was correlated to various social factors. His material shows a higher rate of suicides in the middle group of society. An investigation of New York children [10] points in the same direction. Conditions may possibly be different in the case of Swedish children and adolescents. In this country the low income group (Social group III) is conspicuously preponderant in relation to the average structure of the population. It should be noted, however that it is difficult to make comparisons between different countries. In the present survey Social group III is heterogeneous socially as well as economically.

The variability in the incidence of suicides in different countries is greater in children and adolescents than in adults, and greater in younger than in older adolescents. This seems to indicate that external factors are more important to children and adolescents than to adults [5]. The importance of behaviour and development of the individual in his environment during childhood and adolescence is well known, and it is certainly not coincidental that the family environment was noteworthy in a large number of cases (96 %). It is not possible to determine from this series however whether constitutional or exogenous factors were more important in the decision of the children to make suicidal attempts. It has been suggested that a specific hereditary factor is present but this is contradicted by the studies of twins made by Kallman and his associates [11]. That environmental factors play a role is shown by the fact that there is a relatively high incidence of attempted suicides among the youth of big cities. In connection with Sainsbury's observations on social isolation and mobility as factors of importance for provoking suicidal attempts, it is interesting to note that 78 adolescents or 5 % of the entire material were refugee or "war victim" children from war ravaged countries who were transferred to Sweden and taken care of by Swedish families.

When studying the motives leading to suicidal attempts, one is faced with a series of difficulties. It has been established that the motive mentioned by the patient immediately after his suicidal attempt often differs from that indicated by him a few days later [6]. The purely psychiatric aspects will not be discussed in detail

here but the difference in the conception of death between children and adults should be mentioned [2]. A young child looks at death in a realistic manner, that is, death means to him immobility and insensibility. In his mind death is a reversible condition. Children, like adults, use suicide as a means of punishing their environment and/or attracting the attention or stimulating the love of those nearest to them. Mulcock [12] has emphasized that the provoking element is often trivial and of little importance in the ensemble of predisposing factors, such as a general lowering of mental resistance due to difficult conditions of growth and environment, lack of love, adjustment difficulties of various kinds, abnormal personality traits, mental illness or poor intelligence, a broken home (due for example to divorce or death), sibling conflicts, the feeling of being excluded and unwanted, school difficulties etc. These considerations must be kept in mind when the causes of suicidal attempts by children and adolescents are discussed, and it should be underlined that the reasons recorded in the tables of the present survey have in many instances been noted in the hospital records in cases where no thorough psychiatric examination was made.

The method used in attempting suicide also deserves comment. Hartelius has called attention to the increase in the number of suicides committed by women and to the growing use of drugs, discussing the possibility of a connection between the two factors. It is known that women are more apt to use passive methods, such as taking tablets, while men prefer more active means. This is in agreement with the fact that men are responsible for a larger part of the completed suicides, whereas the incidence of suicidal attempts is higher among women. The tendency of males to use violent methods such as hanging and strangulation, using firearms and edged weapons etc. is noticeable in children and adolescents as well. The preponderant place of the consumption of drugs as a method of suicide is apparent in the investigation made in Stockholm by Ettlinger & Flordh. In 73 % of 500 suicidal attempts drugs belonging to the barbiturate group had been used. Nearly 8[illegible] of the subjects in the present survey used drugs, mostly barbiturates. Boys constituted almost 18 [illegible], a figure which corresponds closely to their share in the total number of suicidal attempts. This suggests that below the age of 21 years there is hardly any difference between the sexes as regards the use of drugs. Other methods of suicide constitute a rather insignificant proportion of the total number, 13 [illegible] altogether. Under the heading "Other" are grouped *inter alia* taking trichloroethylene, sublimate, carbon tetrachloride, nicotine solution and ammonia. Among the patients were a haemophiliac provoking his bleedings, a diabetic injecting himself with too big doses of insulin and several who had eaten cigarettes.

There are good reasons for assuming that suicidal attempts in boys should be considered more serious than in girls. More boys require continued psychiatric treatment. This is in accordance with the interpretation of mental disorders behind their suicidal attempts (Table 3) as being more deep-seated in many cases. The incidence of recurrence also seems to be somewhat greater for boys. For most girls, on the other hand, suicidal attempt

seem to be impulsive acts connected with seemingly rather insignificant, acute mental traumata such as love conflicts. A further impression derived from the present survey is that girls are often not considered as deviating mentally or being disturbed after their suicidal attempt. It is possible however that the difference between the sexes is more apparent than real or in any case not so marked as is often imagined. Presumably at least some cases are misjudged because of the more introverted reactions of girls to mental stress through depressive tendencies, psychomotor disorders, etc. The reactions of boys, through aggressiveness, destructivity etc. are more conspicuous to their environment and thus more easily interpreted as being serious. It can, therefore not be excluded, that the higher frequency of completed suicides committed by boys depends, at least in part on a more fatal choice of suicidal method, rather than on a more serious mental disorder in comparison with the disorders motivating the attempts made by the girls.

Summary

Data were collected for the five year period 1955–1959 from the hospitals in Sweden on suicidal attempts made by children and adolescents under 21 years. The series includes 1727 patients (351 boys and 1376 girls). The age distribution, the seasonal variations, the annual rate the social background, the school conditions, the family situation, the reasons for the attempted suicides and the method employed are recorded. In accordance with earlier observations, it was established that the frequency of suicidal attempts increased with age and sex (higher in girls than boys). During the period 1955–1959 the absolute number of attempted suicides increased considerably. The relative frequency showed, however a less marked increase. The majority of the patients (83%) belonged to the low income group (Social group III) and had a difficult family situation in many cases.

Among the reasons indicated for the suicidal attempts, love problems were clearly predominant (30%) followed by family problems (25%). Certain differences existed between the boys and the girls regarding the motive. The difficulties of finding the true background of a suicidal attempt where no thorough psychiatric examination is made are emphasized. By far the most common method used was the ingestion of various drugs (87%). Certain circumstances seem to indicate that the suicidal attempts made by boys are more serious than those by girls. The boys use more active and violent methods; they are considered to need continued psychiatric treatment more often, and the frequency of repeated attempts is higher than in girls. It is possible however that this difference between the sexes is more apparent than real, or not so marked as is often supposed.

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Departments of Paediatrics and Child Psychiatry
Kronprinsessan Lovisas Barnsjukhus
Polhemsgatan 30
Stockholm K
Sweden

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From the Department of Virology University f Helsinki, and Aurora Hospital, Section III Helsinki, Finland

Virological Diagnosis of Measles[1]

by PEKKA HALONEN OSSI PETTAY and IRJA SALMI

The question which prompted the present study was. What is the diagnostic value of serological studies and measles virus solation as a routine practice at hospitals for infectious diseases? A good opportunity for the study arose early in 1960 when a measles epidemic occurred in Helsinki.

Since the original report of Enders & Peebles in 1954 [9] on the isolation of a filtrable gent from measles patients in human kidney tissue cultures, many in vestigators have succeeded in isolating measles virus [* 7 10-1.. 14 15 17 10 *0]. In studies on the epidemiology of measles, the value of serological methods, especially the complement fixation tech nique has been clearly demonstrated [1-4 9-11 14 15 10].

The clinical diagnosis of measles is al most always a simple matter but there are a certain number of cases which present diagnostic problems. It was felt that here specific virological diagnosis might prove of value t hospitals for infectious diseases.

Materials and Methods

Collection of specimens for virus isolation nd serological studies

The clinical series consisted of 90 patient with measles, 21 having pneumonia, 5 otitis and 1 encephalitis as complications.

[1] This study was supported by grants from the Sigrid Jusélius Foundation.

The first blood specimen for serological studies wa taken on admission or the fol lowing day The second specimen was taken 7-10 days later and the third from some of the patients one month after the first. Serum specimens were stored in rubber capped tubes at -20°C for 1-3 months before antibody determination.

Sixty throat swabs and 43 heparinized blood specimens were collected for virus isolation experiments. The throat swabs were taken in 3 ml of Eagle minimum essential medium [8] with 5% horse serum and 5% tryptose phosphat broth containing 200 units of penicillin, 200 mg of streptomycin, and 25 units of nystatin per ml. The speci mens in rubber-stoppered tubes, were stored at 4°C in the refrigerator of the ward for 2 18 hours before transfer with other routine specimens to the virus laboratory During handling and transportation the specimens were t room temperature for 2-4 hours. In the virus laboratory the specimens were inoculated into cell culture tubes im mediately or after storage for 1-6 weeks at -60°C.

Specimens for serological studies were also collected from a control series consisting of 22 children with other infectious diseases, such as poliomyelitis, mumps, and scarlet fever The acut and convalescent phase serum specimens were collected within 7-10 days.

Cell cult re

Human amnion cells of a continuous line, strain Utrecht, obtained from Dr R. Doorschodt, Hygienisch Laboratorium der Rijks Universiteit, Utrecht, Holland, were grown in a 0.5% lactalbumin hydrolysat

medium with -5 % calf serum. At the time of inoculation the tubes were washed twice with Hanks solution and 1.0 ml of the maintenance medium was added. Two types of maintenance media were used for amnion cells: 5 % horse serum, 5 tryptose phosphate broth, 90 % Eagle's minimum essential medium and 5 % calf serum, 20% bovine amniotic fluid, 5 % modified medium no. 199 (without vitamins, purines, pyrimidines, riboses or cholesterol).

Human embryonic kidney and primary amnion cell culture tubes were prepared by the standard trypsinization techniques. Kidneys of embryos 2-4 months old were used. The growth medium of kidney cultures was 10 % human serum in Eagle minimum essential medium, and the maintenance media 5 % calf serum, 20% bovine amniotic fluid, 35% modified medium no 199 and 45 % Earle's solution or medium no. 199 without serum.

The maintenance media in the tubes were changed once or twice a week. All cell culture media contained penicillin, streptomycin and nystatin in the concentrations indicated above.

Virus strain

The measles virus strain was obtained in 1959 from Dr L. Philipson, Institut of Virology, University of Uppsala, Sweden.

Complement fixation test

Complement fixation tests were made by Bengtson technique with minor modifications [13]. Measles virus antigen was prepared in amnion cell cultures in Roux bottles containing 60 ml of maintenance medium. After complete degeneration of cells had taken place usually 7 days after virus inoculation, the medium with the degenerated cells was harvested and stored at -20°C. The antigen titers in the several lots prepared were between 1:4 and 1:16 against 8 antibody units and full unit of complement. No antigen was anticomplementary. A control positive human immune serum was included in each CF test. The CF titer of the control serum was usually 1:64 but varied by one tube up or down in a few of the tests.

Inoculation of specimens

From each specimen for virus isolation 0.1 ml was inoculated into 4-6 cell culture tubes. The tubes were incubated for 3-8 weeks at 36°C and microscopical examination was made twice a week. Before the tubes were discarded one or more tubes from each isolation specimen were fixed in Bouin's fixative and stained with hematoxylin-eosin by the collodion membrane technique [9].

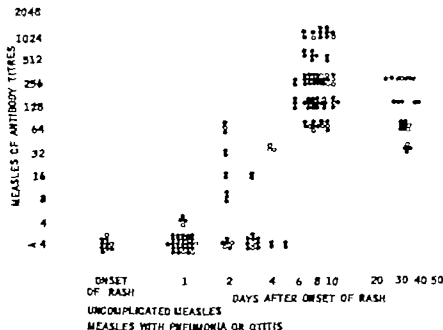
Results

Complement fixing antibody titers in measles patients. CF titers of all measles patients are plotted in Fig. 1. No specimen taken the day the rash appeared had CF antibodies in a dilution of 1:4 or higher. One day after the onset of the rash 7 of 34 specimens were positive; in 2-4 days about half the specimens were positive and in 6 days and thereafter all specimens were positive. The peak was reached in 10-20 days when the titers were between 1:64 and 1:2048. After 3-4 weeks the average values of the titers began slowly to drop. The rise in titer was at least fourfold in all the patients if the first serum specimen was taken within 5 days of the onset of the rash.

A high CF titer 1:1024 or 1:2048 was encountered in 6 of 65 among the uncomplicated cases and in 11 of 23 among the cases with complications.

Complement fixing antibody titers in patients with measles and other concurrent virus infections. Three patients with measles apparently had two virus infections simultaneously. Two had been vaccinated against smallpox and developed a

FIGURE 1 MEASLES COMPLEMENT FIXING ANTIBODY TITRES OF ACUTE AND CONVALESCENT PHASE SERUM SPECIMENS OF 90 MEASLES PATIENTS



primary reaction a few days before the measles rash appeared (Cases 1 and 2). Their CF antibody responses were of the usual type. In both patients the clinical picture was mild. One of them even had a third virus infection, chicken pox, just before the vaccination reaction appeared

The third patient had parotitis and later serous meningitis apparently caused by the mumps virus, at the same time as the measles (Case 4) The measles CF titers rose rapidly in her serum specimens, increasing in 7 days from below 1 4 to 1 51_ No mumps CF antibodies could be detected in either specimen (mumps titrations were carried out at the State Serum Institut Helsinki). Unfortunately the convalescent phase serum specimen was taken only 8 days after the onset of the parotitis.

Complement fixing antibody titers in other patients with infectious diseases In the acute and convalescent phase serum specimens of 2_ patients with other infection diseases no increase in measles CF antibody titer was observed. Sixteen patients had measles CF antibodies; a twofold decrease in titre was observed in two serum pairs

Attempted virus isolations Twenty five throat and 20 blood specimens were selected for isolation xperiments. They were all taken on the day of or the day following the appearance of the rash. Each specimen was inoculated into human mbryonic kidney and amnion (primary and continuous) cell culture tubes

No agents inducing the formation of syncytial or giant cells were isolated. Ser

eral specimens were passaged blindly once in cell culture tubes after incubation for 3–6 weeks in the primary passage Two viruses with enterovirus-like CPE were isolated from throat specimens.

In the tubes inoculated with the control measles virus a typical formation of syncytial and giant cells was observed and in histological examination large eosinophilic intranuclear inclusions could be seen

Discussion

The results of the present study indicate that serological diagnosis may be the only feasible way to make a specific virological diagnosis of measles as a routine at hospitals for infectious diseases

For serological diagnosis of measles the complement fixation technique seems to be reliable since in each of the 90 acute and convalescent phase serum pairs tested a significant increase in CF titer was obtained if the specimens were taken at suitable times The titers began to rise 1 to 6 days after the onset of the rash and a slow drop began in 3–4 weeks and according to other studies [1 3 4 11] CF antibodies remain permanently at a detectable level. Therefore the first serum specimen should be taken within 5 days of the onset of the rash and the second " 14 days later The specificity of the measles CF test was shown by the lack of increase of titer during other infectious diseases.

The diagnostic value of this test was further emphasized in two cases. One was clinically diagnosed a German measles but by serology wa proved to be measles (Case 4) In the other patient a morbilliform rash appeared after smallpox vaccination (Case 3). A diagnosis of measles wa made but in serological examination no rise in CF titer occurred. After re-examination of clinical data the ra h and other symptoms were considered to have been caused by the vaccinia virus. In two patients with measles with simultaneous vaccinia infection a significant rise in measles CF antibody titer was observed Another use for measles serology is in detecting subclinical infections, for instance in patients who have received gamma globulin [6].

The entirely negative results of the attempts at measles viru isolation in the present study may be explained by the type of cultured cells used. Enders *et al* [10], and Mitus *et al* [15] have reported a failure to isolate measles virus in amnion cells, whereas from the same specimens virus was recovered in human kidney cell cultures. The second factor which should be considered is the synthetic maintenance medium used in our human kidney cell cultures which was different from that used by Enders. As shown by Reissig Black & Melnick [18], completely different cytopathogenic changes may be produced by the measles viru depending on the cell culture media employed. Furthermore the handling and storage of the specimens may have been one of the most important reasons for failure to isolate the viru [5 10]. The difficulty of measles virus isolation and the long incubation period often necessary for the appearance of CPE may make this procedure suitable only for special cases e.g for autopsy material.

Case Reports

Case 1 A boy aged 7 vaccinated with vaccinia viru on February 3 1960 responded with a normal primary reaction. On

February 15, when the vaccination reaction still persisted, catarrhal symptoms appeared and on February 19 typical measles was diagnosed. The rash was especially dense around the scar with a narrow free zone in between. Recovery was uneventful. His measles CF titers were: February 20 1/<4 February 27 1/256; April 5, 1/64.

Case 2 A boy aged 1 year 11 months was vaccinated on February 3 1960. Three days later he exhibited an eruption, which his mother diagnosed as chicken pox. Considering epidemiological data and the appearance of the scars later on the diagnosis was probably correct A normal primary reaction ppeared on about the 8th day after vaccination. On February 19 he was admitted to the Aurora Hospital with typical measles. The disease was mild and recovery uneventful. His measles CF titers were: February 20, 1/<4; February 27 1/128

Case 3 A girl aged 1 year and 3 months was vaccinated on F bruary 5, 1960. A week later simultaneously with the primary reaction, morbilliform rash appeared. On admission the next day slight catarrhal symptoms were observed but no Koplik spots. The temperature was 37.8°C but fell t normal within day Owing to the prevailing measles epidemic and the rash, the case was diagnosed as measles. However in the serological studies no measles CF antibodies could be detected, even during convalescence In re-evaluation we believe it probable that the rash was, in fact caused by the vaccinia virus.

Case 4 A girl aged 4 was known to have had repeated contact with both measles and mumps patients. She manifested catarrhal symptoms of the upper respiratory tract on March 1960. Two days later she was feverish and the parotid salivary glands began t swell. On admittance, on March 10 she had a rash, which was diagnosed as German measles In addition, her parotid glands were very swollen and their consistency resembled that found in mumps. Her admission temperature was 39.0°C. It fell to normal within two days but rose again and serous meningitis was diagnosed. The cell count in the spinal fluid was 715/mm³ 68% of which were mononuclear cells. The temperature remained slightly elevated for about ten days. In two weeks the child was well again. In the serological tests the measles CF titers rose from 1/<4 to 1/512, which proved the case to have been one of measles. In spite of the typical clinical picture no mumps CF antibodies could be detected in either specimen.

Summary

The value of specific virological diagnosis of measles as a routine practice at hospitals for infectious diseases was studied.

Serological diagnosis by the complement fixation technique proved to be reliable since in all 90 cases studied a significant increase in titer was observed during the course of the disease if serum specimens taken at suitable times were compared no increase in titer was observed in serum pairs from 22 patients with other infectious diseases.

No measles virus was recovered from 25 throat swabs and 20 blood specimens taken less than 24 hours after the onset of the rash in cultures of primary trypsinized human amnion or human embryonic kidney cells, or of human amnion cells of a continuous line.

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Department of Virology
U iversity of Helsink
Fabianinkatu 4
and Aurora Hospi al
Nordenskiöldinkat I
H lsinki
Finland

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From the Department of Paediatrics (Head: Professor Bo Vahlquist) University Hospital, Uppsala, and the Institute of Virology (Head. Professor Tore Wesslén) University of Uppsala, Sweden

Sero-Immune Patterns for Poliomyelitis and Mumps in Children of Nomad Lapps

by TORE MELLBIN

The incidence of antibodies to poliomyelitis among different age-groups and populations has been the object of numerous investigations. These have been designed to elucidate the rising age at which persons become affected by clinically manifest poliomyelitis as social standards improve and, before introducing widespread immunization to the infection, to gain an impression of the incidence of spontaneously developing antibodies.

It has been shown in many investigations carried out in tropical and subtropical regions [2–5, 8 10 13–15] by a variety of methods that the incidence of poliomyelitis antibodies is very high even at an early age Paul & Horstmann [15] found antibodies to one type of poliomyelitis in 87–95 % of Casablanca children aged 5–9 years and antibodies to all three types among 78 %. The increase in antibodies commences immediately after the maternal antibodies disappear which means that the virus is heavily distributed throughout the local community Gajdusek, Rogers & Bankhead [3] reported similar findings among children of the same age group from the jungles of Bolivia and Peru. all *6 children whom they examined had antibodies to all three types of poliomyelitis virus. Investigations carried out in Tahiti Mexico Egypt the Congo, the Middle East, and other areas show similar results. The high incidence of antibodies to poliomyelitis virus in these regions is partly associated with the low social standards prevailing there The poor state of hygiene and the density of the population, the people living in overcrowded, primitive dwellings cause widespread dissemination of infection The difference between the incidence of poliomyelitis antibodies between population groups of differing social standards but living in the same area has been demonstrated by Melnick & Ledinko [7] and others.

Paul and his collaborators [11 12] have examined the incidence of poliomyelitis antibodies among Eskimos living on the north coast of Alaska and report quite different findings They found 5 % of children aged 4–9 years to have antibodies to Type I 3 to Type II, and 10 % to Type III A high incidence of antibodies was only recorded among adults. The low incidence among Eskimos is probably due to the isolation of this people and its dispersion over a wide area

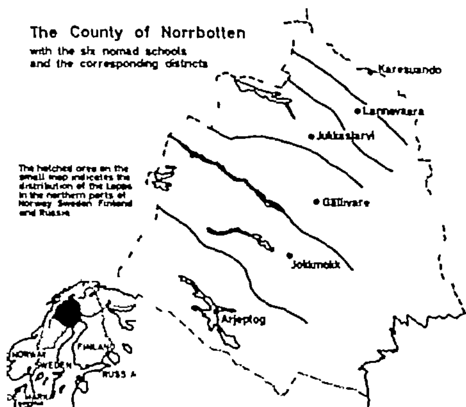


Fig 1

The incidence of mumps antibodies too, varies in different populations Paul Riordan & Kraft [11] found positive complement fixation reactions among 39 of 23 Alaska children aged 5–9 years Gajdusek, Rogers & Bankhead [3] reported positive titres in 61 of a series of Peruvian children of the same age Since in person who have suffered from mumps these complement fixation titres fall fairly quickly the figures must be regarded as minimum figures

The nomad Lapps have a characteristic mode of life In connexion with other investigations on the children of Lapps living in the county of Norrbotten, Sweden (see map Fig 1) the incidence of poliomyelitis and mumps antibodies was therefore examined Because these families are repeatedly flitting, following their herds of reindeer they have at least two and often more dwellings. During the summer they are isolated in the fells, in winter they commonly live in small inland villages They are therefore in most respects all the year round more isolated than the sedentary population This isolation has lessened during recent years especially in the more southerly regions but in the north it is still fairly considerable Like other Swedish children those of the nomad Lapps start going to school when they are 7 years old Owing to the great distances, boarding schools are provided where the children live during term time

Investigations into the incidence of

TABLE 1 *Confirmed cases of poliomyelitis in the county of Norrbotten during 1949–1958*

Year	Total number of cases in the county of Norrbotten	Number of cases in the regions inhabited by the Lapps
1949	33	8
1950	29	5
1951	18	2
1952	4	1
1953	74	10
1954	31	0
1955	14	
1956	5	0
1957	14	0
1958	0	0

poliomyelitis antibodies among the population of Norrbotten county were carried out by Olin & Wesslén [9] on specimens collected in 1954 these formed part of a major investigation embracing five different regions of Sweden. The Norrbotten material was obtained largely from populations of towns in the south-eastern part of the county Surprisingly high antibody titres were found in this part of the series compared with the other regions, of 8-year-old children 76 % showed antibodies to Type I 82 % to Type II, and 51 % to Type III only 2 % of these children gave negative findings, and 32 % had antibodies to all three types. The authors suggest that these high figures may partly be explained by the fact that most of the area in which the specimens were collected obtains its water supply from the same river

The incidence of antibodies in the parish of Arjeplog south western Norrbotten, was investigated in a small series in 1957 by Dagull [1] who reported that 47 % of children aged 4–10 years had antibodies to Type I 16 % to Type II and 18 % to Type III figures that are much lower than those reported by Olin & Wesslén for the town populations of the coast.

Lapinleimu [6] examined the incidence of antibodies in northernmost Finland (Kemijärvi, a country district) and found among children aged 5–9 years that 71 % had antibodies to Type I 58 % to Type II and 42 % to Type III, antibodies to all three types were present in 20 % of the children.

The incidence of clinical poliomyelitis in Norrbotten county during the lifetime of the children included in the present investigation is shown in Table 1 About 230,000 people reside in the county and the density of population is 2.4 inhabitants per sq km (6 1 per sq mile) As can be seen the figures are very low except for 1953 when there was a major epidemic in Sweden

The investigation now described was limited to children going to school for the first time that is, children who had previously led an isolated existence It would, of course have been opportune having regard to the mingling of the children at the boarding schools, to have traced the antibody levels during the seven years

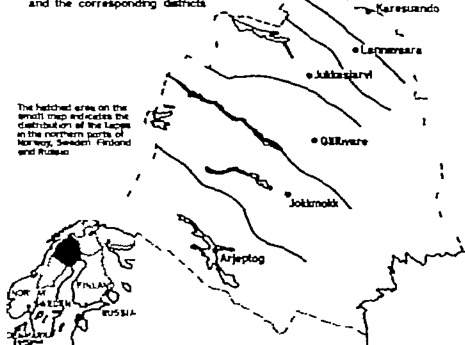


Fig. 1.

The incidence of mumps antibodies, too, varies in different populations. Paul, Riordan & Kraft [11] found positive complement fixation reactions among 39 % of 23 Alaska children aged 5–9 years. Gajdusek, Rogers & Bankhead [3] reported positive titres in 61 of a series of Peruvian children of the same age. Since in persons who have suffered from mumps these complement fixation titres fall fairly quickly the figures must be regarded as minimum figures.

The nomad Lapps have a characteristic mode of life. In connexion with other investigations on the children of Lapps living in the county of Norrbotten, Sweden (see map, Fig. 1), the incidence of poliomyelitis and mumps antibodies was therefore examined. Because these families are repeatedly flitting following their herds of reindeer they have at least two and often more dwellings. During the summer they are isolated in the fells; in winter they commonly live in small inland villages. They are therefore in most respects all the year round more isolated than the sedentary population. This isolation has lessened during recent years, especially in the more southerly regions, but in the north it is still fairly considerable. Like other Swedish children, those of the nomad Lapps start going to school when they are 7 years old. Owing to the great distances, boarding schools are provided, where the children live during term time.

Investigations into the incidence of

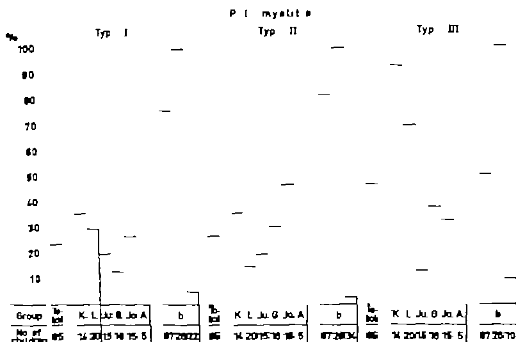


Fig. 2. Antibodies to poliomyelitis virus Types I, II, and III. Percentage distribution of children with positive titres in the Lapp series and in series for comparison. K. = Karesuando, L. = Lannavaara, Ju. = Jukkasjärvi, G. = Gällivare, Jo. = Jokkmokk, A. = Arjeplog. = children from Norrbotten county Sweden (8 years of age) [9], b = children from Peru and Bolivia (5–9 years of age) [3]. = children from Alaska (4–9 years of age) [12].

2 The figure also shows three series for comparison, one of Swedish children from south-eastern Norrbotten, one tropical series, and one arctic series, all composed of children of similar age The incidence of antibodies in the Lapp children included in this investigation is low This is particularly true of Types I and II, against which antibodies were present in only 24 % and 27 % of the whole series, respectively Type-III antibodies were found in 47 % of the whole series. The higher figure is explained by the fact that these antibodies were present in a very high proportion of the children at the two most northerly schools (93 % and 70 %), the other schools showing figures of the same order as those for the Type-I and Type-II antibodies. This difference between the two northernmost schools and the other four is highly significant (0 001 > P) With regard to Type-I antibodies, too the highest incidence is found in the two northernmost schools, and in the Karesuando school, the most northerly situated of them all, the incidence of Type-II antibodies was also relatively high.

All Karesuando children showed antibodies to one or more virus types, whereas no child from Arjeplog, the most southerly of the schools, had antibodies to any type of virus (the number of children at this school was very small). The difference between 3-negative children from the

TABLE 3 *Antibodies to poliomyelitis virus Distribution of children according to antibody titre.*

Type	N of children	Titre <2	3–4	6–12	16–32	48–96	>128
I	83	65	11	5	2	1	0
II	86	63	7	2	7	4	3
III	85	45	8	10	1	6	4

two most northerly school districts and from the four other districts is significant $(0.001 < P < 0.01)$. Only *four* children (5 %) out of the whole series had antibodies to all three types of virus and three of these were from the two most northerly districts.

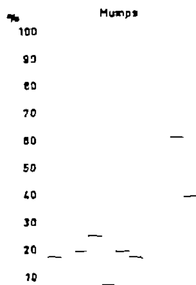


Fig. 3. Antibodies to mumps virus. Percentage distribution of children with positive titres in the Lapp series and in series for comparison. K.–Karesuando L.–Lannavaara, Ju.–Jukkasjärvi, G.–Gällivare Jo.–Jokkmokk, A.–Arjeplog a–children from Peru (5–9 years of age) [3], b– children from Alaska (4–8 years of age) [11].

The distribution of the titres for the whole series can be seen from Table 3. Type III shows the highest incidence and the highest titres and Type I the lowest.

Mumps

The incidence of antibodies is shown in Fig. 3 which also includes two series for comparison, one from the tropics and one from the arctic. The incidence of antibodies is low. It is highest in Lannavaara (25 %) and lowest in the little group from Arjeplog (no antibodies demonstrated). The incidence for the whole series was 17 %.

The distribution of the positive titres can be seen from Table 4. The series is here arranged in two groups, the three northernmost and the three southernmost schools. The proportions of children with antibodies are similar 18 % and 15 % respectively but the titres are rather higher in the southern group.

Discussion

Before starting school the children of nomad Lapps live under isolated conditions, a fact that is clearly reflected in the findings now reported. The incidence of antibodies to poliomyelitis and mumps virus is very low compared with other

TABLE 4 *Antibodies to mumps virus Distribution of children according to antibody titre*

Region	No. of children	Titre						
		< 20	20	40	80	100	160	320
The 3 northerly schools	50	41	3	2		0	2	0
The 3 southerly schools	40	34	0	1	0	1	3	1
Total	90	75	3	3		1	5	1

populations, both in Sweden and elsewhere previously investigated.

The incidence of antibodies to poliomyelitis virus Types I and II is only one-third of that in children of the same age-group living in the coastal region of the same county [9]. Of the Lapp children 32 % had no poliomyelitis antibodies, and 5 % had antibodies to all three types. The corresponding figures for the children from the coast were 2 % and 32 % respectively in other words the figures are changed about.

The two most northerly school districts Karesuando and Lannavaara differ from the others. This divergence concerns particularly Type-III antibodies, which were present in 93 % and 70 % of the children at these two schools respectively These children also showed the highest incidence of Type I antibodies, although in thi instance the predominance was less marked. Only four of the 34 children in this region (12) had no poliomyelitis antibodies, compared with 45 % in the other four regions combined.

The low incidence of clinical poliomyelitis in the county of Norrbotten compared with other parts of Sweden is associated with the high incidence of antibodies in the relatively densely populated south eastern parts of the county The Lapp children, on the other hand have very low immunity but the geographical isolation has resulted in a low incidence of the infection within the regions inhabited by the Lapps. It is difficult to explain the high incidence of antibodies in the northernmost districts, where the population is scattered over wide areas in very small villages, and where there is little mixing between the inhabitants of the two districts The water supply in these regions comes from local wells and various rivers No known case of poliomyelitis has occurred since 1953

The incidence of antibodies to mumps virus is also low and is still less than that in Alaskan Eskimo children of corresponding age [11] This is the more striking since the published figures for the Eskimo children refer to complement fixation titres, and may therefore having regard to the rapid disappearance of these titres after the infection, be regarded a minimum values. The poor immunity of the Lapp children to mumps and also to other virus infections results in repeated, comprehensive epidemics at the nomad boarding schools

Summary

The incidence of antibodies to poliomyelitis and mumps w investigated in nomad Lapp children who had previously

lived under isolated conditions, entering school in autumn 1957 and 1958 The inci dence of poliomyelitis antibodies was low (Type I 24 %, Type II 27 %, and Type III 47 %) and was highest in the two northern most school districts (especially Type III)

The incidence of mumps antibodies was also very low being only 17 % for the whole series

Acknowledgments

My thanks are due to Professor Tore Wesslén and Docent Lennart Philipson for carrying out the antibody titrations and for their valuable advice. The in vestigation was supported by a financial grant from the Norrbotten County Coun cil, Sweden.

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Department of Paediatrics
University Hospital
Uppsala
Sweden

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From the Children's Clinic and the Child Psychiatric Clinic, the County Central Hospital, Örebro, Sweden

Chronically Disturbed Children

Studies of the Incidence and the Care of Children who are Chronic Invalids[1]

by OLOF BRANDBERG and BENGT RUNDBERG

Introduction

During recent years a greater interest in the frequency and care of children who are chronic invalids[2] has been taken. Although Sweden possesses many modern facilities for the care of these children much remains to be done in the area of socio-medical "rearmament Perhaps the most important is to assure that all young people including the group who for different reasons are presently excluded achieve improved and above all, proper care.

Doubtless in the past there were more forgotten and 'hidden away children than at present owing to the increasing development of child welfare and medical care in Sweden.

It is difficult to predict the favorable impact of comprehensive rehabilitation for these children in the community because therapy progressively is more specialized and specific for many types of defects and injuries. Take for example congenital heart disease which, through methods introduced during recent decades, can often be diagnosed and treated in a way that formerly would have appeared almost inconceivable We may also mention the progress made in orthopedics in the correction of deformities such as clubfoot and congenital dislocation of the hip Still another example are the increasingly refined results in the treatment of defects of the lips and palate In addition to the children with somatic disability there is an equally large number of children suffering from mental diseases. This is not only a question of children with intelligence defects who require either care because of mental deficiency or teaching in special schools but also children with nervous diseases, mental disturbances causing difficulties in social adjustment and psychoses.

Investigations of the frequency of Swedish children who are chronic invalids have been carried out previously by J Ström [10] by order of the Royal Board of Health, and by Herlitz & Redin [7], who took an interest in somatically diseased children. Dahlberg [2], Larsson & Sjögren (1954) and Herlitz & Redin [6] made

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lived under isolated conditions entering school in autumn 1957 and 1958. The incidence of poliomyelitis antibodies was low (Type I 24 %, Type II 27 %, and Type III 47 %) and was highest in the two northernmost school districts (especially Type III).

The incidence of mumps antibodies was also very low being only 17 % for the whole series.

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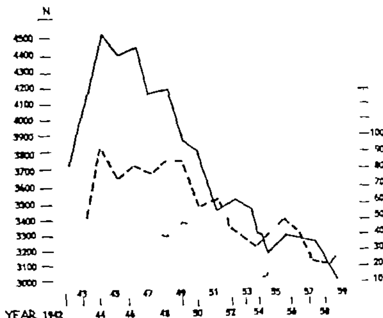


Fig. 1 Number of children, born 1942–1959 now living in the province of Örebro (N) and the number of these who are chronic invalids ( ). ——— total number of children; – – – – our series f chronic invalids; boys in our series.

statistical investigations of the number of mental defectives in certain population areas.

Methods and Material

W have conducted an investigation of the number and care of chronically invalided children (0–15 years) in the province of Örebro, which has 260 000 inhabitants. A questionnaire was prepared and sent t 229 *different organizations: parish registration* offices, boards of hild welfare, child welfare centers, district medical officers and nurses, pediatricians, hospitals, schools, etc. In all, 189 replies were received this proved to in clude all who had been approached because many replied jointly

The number of cases reported was 1146 Upon review 173 of these were discarded as irrelevant. In spite of repeated efforts, we were unable to get into touch with 15 children. Thus 958 hildren remained, these were visited and routine somatic and psychi atric examinations were performed. In many tests were administered in accordance with the Vineland social maturity scale. *Doubtful cases were seen t the hospital for* closer observation and other studies (X-ray examinations, hearing and sight tests, special tests according t Terman–Merrill, etc.) When visits were made the social en vironment which it is most important t observe was noted. Following the examina tions, 77 children were found to be primarily of social interest (mostly children at Child ren s Homes) The final series comprises 681 hildren, 492 boys and 389 girls, who were of socio-medical interest and who were, more-over classified as chronic invalids.

Results

The age distribution of the 958 children is shown in Fig 1 which also shows the total number of children now living in the province who were born during the years 194 –1959 and finally the boys *in the* study A total of 60 000 (59,900) children live in the province. The figure shows that

the highest birthrate was in the 1940 s and that a decrease has occurred in the 1950 s It also indicates a relative paral lelism between the total number of children and the number of cases reported. A predominance of boys over girls was observed. 55.8 % boys and 44.2 % girls.

The material wa further divided into three categories

Children somatically disturbed	320 cases (3' 4 %)
Children mentally disturbed	322 cases (36.5 %)
Children both somatically and mentally disturbed	230 cases (26.1 %)

The children were placed as follows

In Children Homes	83 cases (9 8 %)
In Institutions for Mental Defectives (of whom 63 were "uneducable" and 142 educable")	205 cases (1.5 %)
In special institutions (cerebral palsy hearing defects)	50 cases (5.2 %)
In care outside the province	6' cases (16 6 %)
In family home	541 cases (56.9 %)

Children somatically d sturbed

The group consists of 550 children (0.9 % of the total population). Of these children 230 are also mentally disturbed.

The diseases include the following

W are fully aware that there are more children who are somatically disturbed. However only those who are socio-medical problems are included here. Admittedly demarcation may prove difficul and he figures would be considerably larger if it had been decided to include all the children in the province with, for example diabetes, epilepsy allergy etc. The reason wh man of hese cases are not included is that hey are under regular con rol and, despite their ill ness, heir general mode of life is unimpaired.

	No of cases	
Severe visual defect	2'	(14 boy)
Severe hearing defects	88	(49 boys)
Congenital deformities	181	(100 boys)
Cerebral palsy	104	(63 boys)
Polio sequelae	19	(1 boys)
Other muscle and nerve lesions	9	(4 boys)
Severe epilepsy	5'	(33 boys)
Endocrine disorders	41	(15 boys)

In addition there are diseases of less interest for this investigation, e.g tu mours and diseases of the blood and some allergic diseases

Among the severe visual defects 1 are totally blind and of these _ children have retrolental fibroplasia. Many examples of mild visual defects (strabismus and refractory anomalies) have been observed but are not included in the material.

Of the congenital deformities there are '4 children with congenital heart disease (41 boys and 33 girls) which corresponds to 0 1* % of the total population. In other series (Boston School Survey Cahan, Sampson Rank) the frequency varies from 0.05 to 0 15 % Ma Mahon, McKeown & Record [8] found 633/194 416 live children (0.34). Carlgren [1] reported 0 64 % con genital heart disease among the children of Gothenburg

There are only 6 children with acquired heart disease in our material. The group of congenital diseases includes anomalies of lips and palate thorax deformities lubfoot luxatio coxae etc There are 104 cases (0. boys and 20 girls) of cerebral palsy corresponding to 0 17 % of the total population. This agrees well with Enell's and d Avignon figures given in the Royal Board of Health s report on cerebral palsy [3 4] Herlitz & Redin [6] found 0_1 %

TABLE 1

	Educable mental defectives				Uneducable mental defectives			
	born 1943–52	born 1953–58	born 1 Jan.– 30 Sept. 59	Total	born 1943–52	born 1953–58	born 1 Jan.– 30 Sept. 59	Total
Boys	120	20	2	142	68	26	1	95
Girls	94	11	—	105	45	21	3	69
Total	214	31	2	247	113	47	4	164

Number of children now alive in age-groups 1943–5. 40,465
1953–58 19,4_5

Mentally disturbed children

The group consists of 55? children (0 9 % of the total population) 230 of these were also somatically disturbed. There are 11 psychoses (6 boys) and 84 severe neurotic disorders. The latter group is certainly under represented in the material. As evidence of this, it may be cited that 469 children with neurotic disturbances of different kinds were admitted to the Child Psychiatric Clinic of Örebro in 1959

The majority of children in this group are mentally defective and total 411 cases (see Table 1). After deducting the 6 children born during 1959 this results in a frequency of 0 67 % of the total population for the period 1943–1958 When comparing the figures given in the table with the age curve for the population, it is apparent that we did not succeed in including in the investigation the majority of the educable mentally deficient children of preschool age This is readily explicable, since most of these children first reveal their difficulties at school. In the children born between 1943 and 1952 there were 214 educable morons in a total number of 40 465 children corresponding to 0.53 %, whereas the frequency was only 0 16 % in the children born during 1953–1958 (19,5_5) There is a greater probability that the investigation included a relatively large proportion of the actual number of uneducable children, even those under 7 years of age This number 164 children, corresponds to 0.27 % of the total population. In the age-groups 1943–1952, the uneducables represent 0.28 %. On the assumption that no considerable variations occur in the fundamental causes of mental deficiency the probable frequency of mental deficiency is 0.8 % (educable 0.53 % and uneducable 0.27 %) By comparison, Dahlberg [ ] estimated the frequency of adults with an IQ not exceeding 60 to be 0.5 %, and Larson & Sjögren [9] calculated the risk of morbidity in respect to "low grade oligophrenia" in a rural population of approximately 25 000 persons in Bohuslän (another province of Sweden) at 1 0 % for men and 0 75 % for women. In a very thorough investigation Herlitz & Redin [6] obtained figures of 0 71 % for boys and 0.58 % for girls between the ages of 7 and 11 years.

The "mentally defective group contains 80 children with mongolism (40 boys and 40 girls) which corresponds to 0.13 % of the total population or 1 770 children. None had a mongoloid father or mother

Discussion

The appropriateness of the present form of care

An estimate of the suitability of the present form of care must be by necessity uncertain and subjective An attempt has been made, and the designation "inadequate care" is used in this report when certain essential considerations are present It includes for instance, children whose parents do not permit examinations to be made or treatment that could benefit the child to be given. This term has also been applied to children receiving good care at home but for which the community does not at present possess the necessary resources for care or occupational training Certain others have been stated to be receiving inadequate care if they have stayed in a Community Infants Home for more than one year and if the reason for the prolonged stay is because of difficulty in providing a more appropriate form of care Inadequate care is defined to exist for instance, if children with severe hearing defects, living in a special school for children with such defects also suffer from chronic diseases which have not been thoroughly diagnosed and treated.

Without any doubt the most difficult ta k for us was to judge the adequacy of the care for the children whose mental development has been seriously inhibited Many are well looked after in their homes but the burdensome tasks that this care entails have left a mark on family life Often the parents stat that they do not wish to have more children in other cases brothers and sisters, living at home have to be deprived of the emotional care to which they are entitled, because of their mother s anxiety and concern for the defective child.

We have applied certain rules for such cases. If the child was well looked after in his home and apparently his parents did not find this too onerous and had older healthy children who apparently had not been adversely affected by these conditions, or if the parents did not have other children and the birth of other children did not seem probable because of the parents age, we reported the child as receiving adequate care. On the other hand if the care was deficient or the parents were young and had become neurotic because of their defective child, and the possibility of a happy family life existed if the child in question was placed in institutional care we reported the care as inadequate The same applied if the parents were worn out by their anxiety for the child, despite the fact that perhaps they had never directly thought of letting the child be institutionalized.

In some cases the parents disagreed about the placement of the child, the mother bearing the burden of looking after the child was exhausted and really wished to have the child taken care of whereas the father having less responsibility for care did not consider institutional care to be necessary Other factors have also been taken into consideration, for instance, housing conditions. It is frequently easier to look after a child in a house in the country than in a little flat in an urban area

Cases of inadequate care

A total of 180 cases were classified as receiving inadequate care of these 31 had somatic disturbances 86 had mental

TABLE 2

Categories	Institutional care	Home care	Total
Various somatical diseases	3	44	47
Neuroses	5	15	20
Psychoses	9	6	15
Intellectual defects	11	61	72
Morons and idiots with complicated defects	8	10	18
Borderlines at special school for morons	4	—	4
Unfavorable social situations among morons at external school	4	—	4
Total	44	136	180

disturbances and 63 a combination of both. Forty four of the 180 cases were in different kinds of institutions. The others were looked after in their homes (see Table 2)

The investigation demonstrated that there are inadequate facilities for children with chronic somatic diseases for blind children with complicating defects, mentally retarded with complicating defects (especially idiots with epilepsy) and institutions for care and treatment of children with psychoses and severe neuroses. For the last two groups the resources for care in Sweden are quite insufficient. At the schools for morons we found 4 children, who probably could follow the education in special classes for borderlines. At the special day-schools for morons we found some children who ought to attend the boarding school because of the bad social environment in which they lived

The present need of care

Even if this inventory has not included all the children who are chronic invalids it is nevertheless of interest to try to estimate on the basis of the results obtained, the total needs for care that exist in a population of 60 000 children whose ages vary from 0 to 15 years. Therefore table 3 includes all the children who are at present receiving adequate care in the Provincial Institutions, with the exception of Children s Homes, those who are looked after at home and require different kinds of institutional care as well as children who though possessing domiciliary rights, are cared for in institutions outside the province On the other hand the children who in our opinion, are being incorrectly looked after in the institutions of the province are deducted, and instead are assigned to the appropriate types of institution. The figures given may possibly serve as a guide for estimating the number of beds required. We are aware that for certain groups the results are directly misleading However for others, especially the needs for the care of mental defectives and of children suffering from severe bodily defects, there is reason to assume more complete agreement with the actual conditions

Summary

The frequency of children aged 0–15 years who were chronic invalids in the province of Örebro, which has a population of 60 000 children has been studied.

TABLE 3 *Total need of institutional care for a population of 60 000 children between 1 and 15 years of age.*

Type of cases needing institutional care	No of cases	No. per thousand
Educable mental defectives	170	2.8
Uneducable mental defectives	120	_0
Blind children with complicating defect	11	0.2
Cerebral palsies	30	0.5
Deaf children	45	0.8
Blind children	7	0.1
Epileptics	7	0.1
Disabled children	7	0.1
Children with other types of chronic somatic diseases	6	0.1
Neuroses (prolonged care) or children with primary character disorders	16	0.3
Psychoses	12	0._

The purpose of the investigation was to ascertain the existing possibilities for receiving care and the need for care. A total of 1146 children were reported which after review was reduced to 958 (526 boys and 43_ girls) This group included 77 cases (34 boys and 43 girls) which were purely of social interest whereas the remaining 881 children (49* boys and 389 girls) were chronic invalids and, consequently were of socio-medical interest. The series comprised 320 children suffering from somatic diseases (37 4 %) 322 with mental defects (36.5 %) and 230 with a combination of both (26.1 %). There were 407 cases of mental deficiency (educable and uneducable) i.e 0.67 %. Educable mental defectives born 1943–195_ represent 0.53 _ whereas the corresponding category at preschool age was under-represented. Uneducable mental defectives represent 0.27 %. The probable frequency of mental defectives is estimated at 0.8 %. There were 80 children with mongolism or 0 13 % (1 770 children) Cerebral palsy was observed in 104 cases 0 17 %. Eighty-eight children had severe reduction in hearing, 0 14 %. Congenital malformations occurred in 115 cases, 74 of which were cardiac malformations, i.e. 0 1_ %. There were 84 instances of serious behavioral disturbances (neuroses) but the group is considered to be under represented. A study of the appropriateness of the present form of care showed that in 180 cases care was inadequate

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From the Pediatric Department Karolinska Sjukhuset and the Carlslund Institution for Mentally Retarded, Stockholm, Sweden

The Value of Urinary Sediment Examination as a Screening Method in Suspected Cases of Metachromatic Leucodystrophy[1]

M. H. HELFANT M. BÖRJESON and B HELLSTRÖM

Among the various forms of diffuse cerebral sclerosis metachromatic leucodystrophy or leucoencephalopathy has been recognised by certain clinical, biochemical and pathological characteristics [1 –, 7 8 0 10]. The disease has been found to be characterized by a pathologic accumulation of sulphatides (cerebroside sulphuric acid esters). This disease occurs in an infantile a late infantile and an adult type [5, 0 8]; the late infantile type is the one most commonly described.

A familial predisposition suggesting genetic mechanism, probably recessive autosomal, is common. As in most heredodegenerative diseases f the central nervous system the psychomotor development is usually normal until the onset of the disease, which characteristically occurs between the ages of one and two years in the lat infantile cases. Difficulties in walking and general hypotonia are frequently the initial signs, f llowed by progressive evidence of quadriplegia, ataxia, mental deterioration, nystagmus and optic trophy Involvement of both primary and secondary motor neurons occurs varying in different stages and cases, with extensor plantar responses, areflexia or spasticity; terminally a decerebrat rigidity is usually prominent feature. Common convulsions may occur but more frequently tonic or hypertonic fits are present

Autopsy reports with histological, histochemical and biochemical studies have revealed an accumulation of metachromatic material in addition t a demyelination and a disappearance of the oligodendroglia of the white substance. This metachromatic material appears predominantly in the whit matter but deposits of it are also found in the cortical neurons and basal ganglia and even in organs outside the central nervous system such as the renal t bules, the li er and the gall bladder [6 8 11]. These deposits consist of sulphuric acid esters f cerebrosides, also called sulphatides [3 4, 8 9 1*] and evidence indicates that this increased content of sulphatides may result either from a defect synthesis or faulty breakdown f the cerebrosides, caused primarily by an enzymatic defect Therefore the metachromatic leucodystrophies may be labelled as one form of neurolipidoses and may also be characterized as an inborn error of metabolism [8].

Diagnosis of the disease during life is possible by different methods. Austin was the first to describe the method of urinary sediment examination in five cases, all showing the metachromatic material indicating the pathologic changes in the kidneys. More accurate quantitative biochemical methods in which the sulphatides have been identified have now been

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[1] Aided by grant from he United Cerebral Palsy Research and Educational Foundation, U.S.A.

TABLE 1 *Distribution of age groups*

Age in years	Number	
	Females	Males
0– 5	7	28
6–10	23	35
11–15	30	63
16–20	29	37
21–25	11	17
26–30	18	12
31–35	17	3
36–40	4	4
41–45	9	4
46–50	8	3
51–55	5	4
56–60	2	4
61–65	2	3
66–70	2	1
71–75	—	1
	166	208

developed with lipid extracts of urine [1 2 4 9 10]. Metachromatic deposits have been demonstrated in the bone marrow and leukocytes of peripheral blood in at least one family in which the disease occurred and possibly indicate a special mode of transmission (homozygous form of the disease) [3]

Among the laboratory investigations applicable in the living patient the examination of the urinary sediment has been the one most extensively used. This examination is easily performed and has been regarded as both a reliable and a specific method of establishing the diagnosis. The abnormal deposits in the renal tubules are the source of the metachromatic material in the urine the material is demonstrated by its characteristic staining with certain aniline dyes. Austin [1] describing his findings in detail, found several different structures which stained metachromatically (1) large oval granular bodies, 15 to 25 micra long either asymmetric and irregularly outlined, or gathered together in more rounded globular forms similar to a mulberry or cluster of grapes, (2) irregularly outlined small clusters with a diameter of 10 to 15 micra, and (3) clusters of intermediate size or 'mixed granular bodies' Casts and intracellular and extracellular granules were also found. The presence of some of these forms was related to the stage of the disease at the time of the examination. *Metachromasia could be demonstrated* with toluidine blue O methylene blue and thionine The urinary granules were also studied by refraction solubility and electrophoresis techniques.

We wished to evaluate Austin's technique of urinary sediment examination to ascertain its specificity in routine screening procedures and also to detect previously unrecognized cases of metachromatic leucoencephalopathy For these purposes we examined urine specimens from a large number of patients in an institution *for* mentally retarded.

Material and Methods

The 374 patients of this study ranged in age from 1 t 73 years. All were of low mentality with intelligence quotients usually less than 50. Their *intellectual status was* characteristically stable during confinement at the institution, but in a few cases progressive mental deterioration *had* occurred. *The* likelihood of discovering late infantile cases of metachromatic leucodystrophy with its early onset and rapid course seemed negligible but the possibility of finding adult types of more protracted duration *existed* In T bles 1 and are summarized the distribution of age groups, sex, clinical diagnosis, and associated neurological bnormalities of the patients studied.

Specimens of urine voided a few hours

before examination were collected. Ten millilitres were centrifuged in a cone-tipped tube for 10 minutes. After the supernatant was decanted two drops of a 2% aqueous solution of toluidine blue O were added to the sediment. The material was then stirred for minutes and two drops of this mixture were transferred t a glass slide and covered with a coverslip. In some cases one drop f a 10% neutral formalin solution was added before the mixture was placed on the glass slide. The edges of the coverslip were sealed with Canada balsam to prevent drying. Usually only one glass slide was prepared from each patient, but when a suspicious sediment was found several slides were prepared. Each slide was completely examined under high magnification. The slides not immediately examined were placed in a moist chamber In some of the cases where a positive or suspicious finding was encountered a repeat specimen was obtained from the patient Single specimens from two patients showed large amounts of metachromatic material, and urinary collections from these two cases were sent for biochemical sulphatide estimation.[1]

Urine samples from two biochemically and histologically verified cases f late infantile metachromatic leucodystrophy were vailable for comparison.[2] (Cases 1 and 3 in the paper by Hagberg & Svennerholm, 1960)

Results

The results are summarized in Table 3. Positive findings were encountered in 22 patients i.e 9 % of the cases. Urine specimens from these patients all contained golden brown deposits, usually in amorphous clusters but occasionally in granular bodies of various sizes. A light yellow homogeneous, hyaline material was sometimes seen but not accepted as a positive finding because this substance was apparently crystalline The deposits thought to be positive occurred in large amounts in only two cases Most of the "positive" cases showed only a few clusters in each specimen. In the stained urinary sediments from the verified cases of metachromatic leucodystrophy the deposits occurred in larger amounts and had more consistently a mulberry like appearance The metachromatic material from the verified cases had a slightly reddish hue but this staining characteristic was variable. Two urinary sediments in the present study contained a large amount of metachromatic material which was barely distinguish

TABLE 2 *Certain or probable causes of the mental deficiency*

	Females	Males
Prenatal causes		
Heredity	10	12
Mongolism	35	43
Toxoplasmosis	—	2
Syphilis	1	2
Phenylketonuria	1	1
Hypothyroidism	4	3
Microcephalus	4	
Hydrocephalus	3	2
Epiloia	1	—
Probable prenatal injuries (causing cerebral palsies)	7	11
Perinatal cause		
Prematurity		9
Birth injuries	10	18
Postnatal causes		
Early epilepsies	14	8
Status after cerebral trauma	1	1
Status after meningitis or encephalitis	6	10
Psychosis	3	
Unknown	59	77
Total	166	205

The quantitative sulphatide estimation was kindly performed by Dr L. Svennerholm, Göteborg.

Kindly placed at our disposal by Dr B Hagberg, Uppsala, and Dr A. Vamola, Linköping

TABLE 3 *Occurrence of metachromatic deposits in the urinary sediment*

Number of cases examined	374
Positive on a single occasion	13
Repeated with a positive result	3
Repeated with a negative result	10

able from the verified cases. In these two cases the urine was examined on another occasion for total sulphatide excretion which turned out not to be elevated. It must be pointed out that repeat studies of some positive cases including the two last-mentioned were positive in only three cases.

Clinically none of the "positive" cases had exhibited a progressive course and none of them had any associated neurological abnormalities. The two patients whose specimens were virtually indistinguishable from those of the verified cases were adults. One was a man with congenital syphilis and the other a woman with a history of birth injury Their case histories are summarized below

Case 1 This 48 year old man had been treated during the first four years of life for congenital syphilis. His early development was retarded and he did not walk until four years of age H has always suffered from mental deficiency and since the age of five has been confined to institutions for the care of non-educable patients. Bilateral corneal clouding impairs his vision, but otherwise he has no neurological symptoms. Testing with the Vineland social maturity scale shows his S Q to be below 20.

Case 2 This 53 year old woman had been injured at birth during a difficult forceps delivery Her early development was much delayed and for the past 30 years she has been cared for in institutions for non-educable mental defectives. She has a generalized hypertonus and cannot walk without support. She can speak a few words and has had no convulsions. Testing with the Columbia mental maturity scale gives her an I.Q of 20 to 25.

Discussion

The finding of material of shape and staining characteristics similar to that found in the urinary sediment of verified cases of metachromatic leucodystrophy challenges the reliability and specificity of the technique This material was characteristically less abundant and less reproducible on successive examinations, and these false positive tests diminish the value of this method of urinary sediment examination as a screening procedure It has not been demonstrated that the deposits observed in the present study are identical with the sulphatides which are excreted in increased amounts in the urine of patients with metachromatic leucodystrophy Two of the cases which had large amounts of metachromatic material in the sediment did not demonstrate any increased urinary sulphatide excretion by biochemical determination.

Austin [1], in describing his method stated "An extensive background of experience in the artefacts in normal and abnormal urine is essential to avoid false positive or negative interpretations" Among the dangers listed were old urine specimens, heavy urate concentration, pyuria and artefacts Taking into consideration these sources of possible error the author thought that the metachromatic deposits were characteristic and specific This conclusion was based on a selected control series of 110 pertinent cases which showed no suspicion of metachromatic leucoencephalopathy These cases included

parents and unaffected siblings of patients afflicted with the disease cases of heredo-degenerative disease with other types of diffuse sclerosis and patients with renal, hepatic, muscular and miscellaneous diseases.

Hagberg & Svennerholm [9 10] examined three cases of late metachromatic leucodystrophy with studies of the urinary sediment and chemical analyses of urine blood and cerebrospinal fluid. They also examined corresponding material from healthy children and children with cerebral palsy and other diseases of the central nervous system. Large amounts of metachromatic granules and granular bodies were found only in the patients with leucodystrophy However small amounts of metachromatic material, in the form of free granules, were found in preparations from the other groups. An interesting observation was that the quantity of metachromatic material in the cases of leucodystrophy varied from day to day

Urinary excretion of sulphatides biochemically determined, is not pathognomonic of metachromatic leucodystrophy but the excretion in normal or control cases is usually much lower than in affected patients. Austin [4] was able to obtain small amounts of sulphated cerebrosides from kidneys of some control cases. Hagberg & Svennerholm [9 10] found urinary excretion of sulphatides in all normal cases studied including infants children and adults Analyzed in relation to creatinine excretion the excretion of sulphatides in metachromatic leucodystrophy was increased five- to ten fold. A very large sulphatide excretion was found in urines of healthy infants under one year of age and great daily variations were observed. No systematic study of the urinary sediment with Austin s technique in these youngest age groups has been published, but such work would be of considerable interest

In most of the "positive" cases of the present study the golden brown material was present only in small amounts and was not consistently present on repeated examinations. The possibility that this material was only a product of normal sulphatide excretion cannot be excluded, however the two cases which had abundant amounts of this material on one occasion had no biochemical evidence of increased sulphatide excretion. This fact makes it likely that the findings described here must be interpreted as artifacts caused by unidentified substances. Also the golden brown color developed with toluidine blue O has never been satisfactorily explained, for in most histological and histochemical work the metachromatic reaction with toluidine blue O results in a reddish or violet red stain.

It has been established that sulphatides can be identified in the urinary sediment in cases of metachromatic leucodystrophy and that this identification is of diagnostic significance. With repeated examinations, with various staining procedures, and with th precautions outlined by Austin, the observation of large amounts of granular met chromatic material in the urine is reasonably specific. The confirmation of microscopic evidence w th the biochemical determination of urinary sulphatide excretion seems indicated Renal biopsy would likewise be helpful in establishing a definite diagnosis

The use of metachromatic staining of the urinary sediment as a routine screening

procedure in unselected cases and on single occasions is of very limited value the likelihood of false positive results because of artifacts has been underestimated. This is particularly true if the examiner does not have personal experience with the morphological details and staining characteristics of the abnormal urinary deposits found in verified cases of metachromatic leucoencephalopathy

Hagberg's & Svennerholm's finding (1959) that infants normally excrete large amounts of sulphatides in the urine suggests that the occurrence of metachromatic material in urinary sediments in this age group must be studied before its diagnostic significance can be evaluated.

Summary

Toluidine blue O staining of the urinary sediment was evaluated in 374 mentally defective children and adults. Small quantities of golden brown material were found in 32 cases and large quantities in two cases. None of the patients showed clinical evidence of metachromatic leucodystrophy and the two most suspicious cases were retarded by congenital syphilis and birth injury Our findings probably do not represent increased excretion of sulphatides and are thought to be artifacts caused by unidentified substances.

The limited value of this method as a routine screening procedure in unselected cases on single occasions is demonstrated.

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(B.H.) Pediatric Department
Karolinska Sjukhuset
Stockholm 60
Sweden

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From the Pediatric Clinic of the University of Athens

Uropepsin Excretion in Thalassemia

by KONSTANTIN B. CHOREMIS, CHRISTOS A. KATTAMIS and EMMANUEL G. KANAVAKIS

Brüke in 1861 was the first to describe how the urine of normal individuals contains a proenzyme, which by acidification is converted to a proteolytic enzyme identical with gastric pepsin. The name of uropepsin was later applied to this enzyme by Bendersky

The evidence indicates that pepsinogen is produced by the parietal cells of gastric mucosa [2]; most of the pepsinogen is secreted into the lumen of the stomach, where it is converted into pepsin by the action of hydrochloric acid, while another fraction is taken up by the blood stream and is excreted, apparently unaltered, in the urine as uropepsinogen [2].

Disturbances in uropepsin excretion are mainly associated with functional and structural changes of gastric mucosa, and to a lesser degree with functional disturbances of the adrenal and pituitary glands [4 6]. It is a well-established fact that patients with gastric and duodenal ulcers, as well as those with hyperfunction of the adrenal and pituitary glands have an increased uropepsin excretion [4 0]. Uropepsin excretion is absent or very low in patients with gastrectomy pernicious anemia and Addison's disease [7 9 10]. In some cases of iron deficiency anemia and macrocytic anemias slight decreases of uropepsin have been reported [8].

We are not aware of reports concerning the excretion of uropepsin in cases of congenital hemolytic anemias. Because there is hypochlorhydria and reduction of gastric excretion [1] in patients with thalassemia, we have investigated uropepsin excretion in children with this disease

Material and Methods

Thirty children with thalassemia major and 30 hematologically normal children admitted to the Pediatric Clinic of the University of Athens were studied. The normal children were of the same age as the patients which ranged from 4 months to 12 years.

Most of the patients with thalassemia major were known cases and had been given blood transfusions in the past Diagnosis was based on clinical and X-ray findings, as well as hematological examinations (red cell morphology fetal hemoglobin and hemoglobin paper electrophoresis)

Urine was collected over a period of 24 hours. Uropepsin values were estimated by the method of West Ellis & Scott [13] and were expressed in uropepsin excretion units in 24 hours (U P.E.U /24 hrs) in each urine sample

Uropepsin was estimated in duplicate. Urine was always collected before blood transfusions. In some cases uropepsin ex

TABLE 1 *Uropepsin excretion units per 24 hours of patients with thalassemia and controls age 4–24 months (Group I)*

Patients						Controls			
No.	Age in months	Weight in g	Fetal Hb %	Hb g %	U P.E.U 4 hrs	No.	Age in months	Weight in g	U.P.E.U 4 hrs
1.	16	5,890	27 1	4.2	37 4	1.	5	6,250	65
2.	12	9,450	90	2.8	40.0	2.	8	7 720	72.6
3.	24	9, 00	63	4.9	42.5	3.	20	10,550	77 0
4.	12	8,200	53	2.55	46.5	4.	5	5,800	78.8
5.	4	4,100	52	4.9	47.2	5.	12	9,200	79
6.	8	7,950	70	5.69	50.0	6.	8	7,200	96
7	17	7,800	73	2.8	50 0	7	11	10,050	100 6
8.	24	10,680	53	6.30	70.8	8.	22	11,300	102.1
9	5	6,200	60	6.88	75.0	9.	6	7,550	121.0
10.	12	5,800	41.2	5.59	83.0	10.	7	6,600	159
		Mean value			54.6				95.5
		Standard deviation			15.1				25.8
		Range			37 4–83				65–159

cretion was measured before and after blood transfusions, but values of uropepsin were identical. During the investigation some of the patients were readmitted to the hospital for blood transfusion. Uropepsin was always reestimated, but in none of these were significant differences noted.

Patients and control children were divided into two main groups according to their age. Group I consisted of 10 patients and 10 controls, 4 months to 2 years of age. Group II consisted of 20 patients and 20 normal children aged 2 to 12 years.

Results and Comments

Table 1 shows the results from Group I. The 24 hour excretion of uropepsin in children with thalassemia ranged from 37 4–83 U.P.E.U /24 hrs with a mean value of 54 6 units (S.D 15 1) In normal children of this group the uropepsin ranged from 60–159 U.P.E.U /24 hrs with a mean of 95.5 units (S.D 25.8)

In Group I, of 10 children with thalassemia had uropepsin values lower than 50 U.P.E.U /24 hrs while none of the normal children had values as low At the other extreme the highest value in patients was 83 U.P E.U /24 hrs, whereas 5 (50 %) of the controls excreted more than 96 units/24 hrs.

The uropepsin excretion in the patients in Group II (Table 2) ranged from 39.5–260 U.P.E.U /24 hrs, with a mean of 176 units (S D 58) In the normal controls the range was from 101–520 U.P.E.U /24 hrs, with a mean 270.2 units (S D 114)

Two of the patients in Group II excreted less than *100 U.P.E.U /24 hrs, while 10* (50 %) of them excreted between 100–180 U.P.E.U /24 hrs. The highest value in patients was 260 U.P.E.U / 24 hrs. Uropepsin excretion of normal children was much higher 10 (50 %) of them excreted more than 260 U P.E.U /24 hrs.

In most of the children with thalassemia major the excretion of uropepsin was decreased. In a rather high proportion uropepsin values were well below the values excreted by the control group

TABLE 2 *Uropepsin excretion units per 24 hours of patients with thalassemia and controls age 2–12 years (Group II)*

Patients						Controls			
No.	Age in years	Weight in g	Fetal Hb %	Hb in g %	U.P.E.U 24 hrs	No.	Age in years	Weight in g	U.P.E.U 24 hrs
1	2	8,500	48	2.92	29.5	1.	4	16,200	101
2.	8	24,000	24	5.2	60.1	2.	5	19,000	120.0
3.	3	1_,000	71	6.25	122.0	3.	6	20,000	146.0
4.	5½	18,000	63	5.69	125.0	4.	8	26,000	151.0
5.	3	11,000	27	5.15	128.5	5.	6	19,000	164.0
6.	4½	12,500	21	4.2	130.3	6.	9	27 000	185.5
7	3	12,000	48	5.89	161 0	7	9	27,000	200.0
8.	4	14,650	25.2	2.51	165.0	8.	11	30,000	214.2
9.	12	32,000	52	4.45	1 2.7	9	2½	12,300	246.8
10.	6	18,000	23	7.55	172.0	10.	4	18,200	[illegible]
11.	6	16,000	16.6	8.02	175.0	11	7	22,000	276.0
12.	2½	1_,250	26	4.90	176.0	12.	2½	12,350	280.0
13.	8	28,000	[illegible]	5.19	205.0	13.	2½	12,300	290.0
14.	9	27,400	28	5.88	220.0	14.	6	20,400	327.0
15.	8	20,000	70	5.55	220.0	15.	8	25,200	340.0
16.	6	17,250	52	5.64	230.0	16.	10	31 700	352.0
17	11	27,000	21.5	[illegible]	250 0	17	11	32,650	358.0
18.	6	18,200	40	4.43	230.0	18.	6	17,250	464.0
19	6	15,700	28	5.1	235 0	19.	8	23,500	470 0
20	7	19,500	48	6.29	260 0	20.	12	35,400	520.0
		Mean value			1 6				279.2
		Standard deviation			58				114
		Range			29.5–260				101–520

while in the remaining cases the uropepsin excretion corresponded to the lower values of the controls of the same age (Table 3) This difference is also noted in the mean values of uropepsin excretion in both groups In Group I the mean value was 54 6 U P.E.U./24 hrs for the patients and 95.5 U.P.E.U /24 hrs for the controls. The corresponding values for Group II were 176 U.P.E.U /24 hrs for the patients, and 270.2 U.P.E.U / 4 hrs for the controls. Furthermore the highest uropepsin value of a patient was less than the mean value for the normal children in each of the groups.

Discussion

Uropepsin is very low or absent in patients with gastrectomy [9], as well as in conditions associated with destruction of gastric mucosa. Atrophy of gastric mucosa is found in certain types of anemias, most notably in pernicious anemia of Addison–

TABLE 3. *Uropepsin excretion unit per 24 hours in patients with thalassemia and controls in two age groups*

U.P.E.U in 24 hrs	Patients N	Patients %	Normal children No.	Normal children %
	Group I			
0–50		70	0	0
50–100	3	30	6	60
> 100	0	0	4	40
	Group II			
0–100	2	10	0	0
100–140	10	50	4	20
140–200	8	40	4	20
200	0	0	10	50

Biermer in pernicious anemia atrophy of gastric mucosa is also accompanied by complete achlorhydria reduction of gastric secretion and decreased pH of gastric juice [7 10 14] In these patients uropepsin excretion is very low The slight amounts of uropepsin found in some cases are probably produced from the remaining cells of the stomach or from sources other than the parietal cells, such as the white blood cells [7 10 12].

Lumme and co-workers found that uropepsin excretion is decreased by half in patients with anemia due to infestation with the tapeworm *Diphyllobothrium latum* and in other cases of macrocytic anemias. Uropepsin excretion returns to normal after the appropriate therapy for anemia [8]

In a small proportion of iron deficiency anemias achlorhydria or hypochlorhydria and decreased uropepsin excretion was noted. In this type of anemia Rawson & Rosenthal found a moderate degree of atrophy of gastric mucosa [11]

No correlation between uropepsin excretion and severity of thalassemia, hemoglobin values, or percentage of fetal hemoglobin was noted. In some cases the uropepsin excretion was not altered after blood transfusions. Also of interest is the fact that patients readmitted two or three times did not have significant difference in uropepsin excretion, although hemoglobin values were not always the same

When the function of the kidneys, pituitary and adrenal glands is normal, any disturbance in uropepsin excretion is most likely to be due to changes of gastric mucosa. Further investigation is necessary to test the hypothesis that in cases of thalassemia a degree of atrophy of gastric mucosa may exist.

Summary

Uropepsin excretion was investigated in 30 patients with thalassemia major and in 30 normal children of comparable age. Uropepsin excretion was decreased in cases of thalassemia. A good proportion of cases had values of uropepsin well below normal limits, while in the rest the values of uropepsin were in the lower limit of normal. The hypothesis that low values of uropepsin in thalassemia may be due to hypofunction or atrophy of gastric mucosa is advanced.

Acknowledgement

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St Sophia Children Hospital
Athens
Greece

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From the Orthopaedic Department (Head, Prof Carl Hirsch) University of Uppsala, and the Department f Developmental Physiology (Head Prof T Gustafsson) The Wenner Gren Institute f Experimental Biology University of Stockholm, Sweden

Biochemical Studies on the Skeleton of Insulin Induced Micromelia in Chickens[1]

by JOHN A. SEVASTIKOGLOU

Various statistical reports attest to the high incidence of congenital malformations. Investigations by Hertig & Rock [5] indicate that a comparatively large number of early human embryos display malformations of such a character that normal development could hardly be expected. Among 26 human foetuses less than 16 days old, obtained during surgery on the uterus, no less than 12 or 47 % displayed severe abnormalities. MacGregor [9] reviewed 1053 stillbirths and neonatal deaths and found that 20 % of stillbirths and 10 % of neonatal deaths were directly attributable to gross congenital malformations. The frequency of congenital malformations is also relatively high among the survivors (Table 1)

The cause or causes of congenital malformations are more or less unknown. They are however attributed to genetic factors as well as to factors influencing the environment of the embryo During the last few decades experimental teratogenesis has considerably increased our knowledge of the relation of congenital malformations to factors influencing the environment of the embryo Congenital defects have been provoked and reproduced by mechanical influences directly on the embryo and by anoxia or X ray irradiation of pregnant animals. Injections of toxic and bacterial products as well as hormones and other chemicals have also produced a teratogenic effect.

Several works on insulin induced malformations have been published by Landauer [7 8], Zwilling [13], Duraiswami [3 4] and others. A correlation was found between the dosage of insulin and the incidence of limb deformities (Table 2) and between the time of insulin injection during embryonic development and the regional localization of the malformations (Fig 1)

In spite of these and other extensive morphologic studies there is almost nothing known on the way the teratogenetic factors induce the malformations nor how the evolution of the malformations during the embryonic development is reflected by the chemical composition of the organs

The author could find no report of such a systematic study in the available international literature Anderson and coworkers [1] published the results of a comparative morphologic and biochemical study on normal and insulin-injected

[1] Read t the Annual Meeting of the Swedish Orthopaedic Association, Stockholm, December 2, 1960.

TABLE 1

	Total births	Malformations soon after birth (‰)	Malformations 9 months later (‰)	Malformations 5 years later (‰)
Incidence of congenital malformations (per 1000 total births)				
Swedish data (BÖÖK, 1951)	44 109	11 18	—	—
Japanese data (NEEL, 1948)	64.570	12.22	24.84	—
English data (McKEOWN & RECORD 1960)	56.760	17.30	—	22.06

Incidence of some skeletal congenital malformations in ‰

	Swedish data		Japanese data		English data	
	Soon after birth	Later	Soon after birth	Later	Soon after birth	Later
Spina bifida	1.00–1 43	—	0.26	0.32	2.60	2.00
Clawfoot	2 79	—	1 10	1 40	3.93	4.44
Dislocation of hip	0.00	—	0.31	13	0 02	0.67

chicken embryos. This work is based principally on histochemical determinations performed on the growth cartilage of chick embryos shortly before hatching. The authors found some morphological differences of the cartilage of the injected and control embryos. However they observed no differences in the glycogen content and the metachromatic properties of the examined cartilages. Nor were there any differences in the up-take of radiosulphate or the alkaline phosphatase and the phosphorylase activities.

TABLE 2 *Relationship between the dose of insulin and the incidence of deformities of the limbs according to Duraiswami [3]*

Dose of insulin I U	Percentage of all types of deformities of the limbs
1	20.2
1.5	32.2
2.5	46.0
3	65.0
6	90.6
Controls injected with same volume of saline	2.2

An experimental work has been undertaken by the author in order to study the chemical composition of the skeleton during the normal embryonic development of the chick. Furthermore similar studies have been performed in insulin

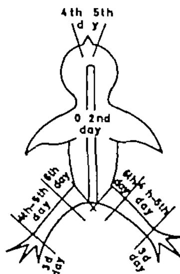


Fig 1 Site of deformity induced by insulin related to time of injection into the egg after incubation [3].

Acta Paediatrica 51: 60–64, Jan. 1962

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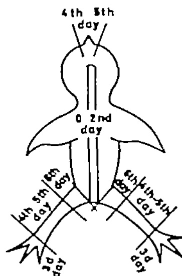


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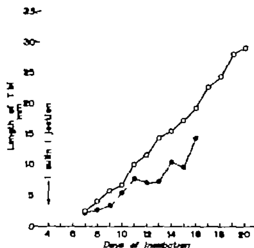


Fig 2. Length of tibiae in insulin injected (broken line) and control embryos (continuous line)

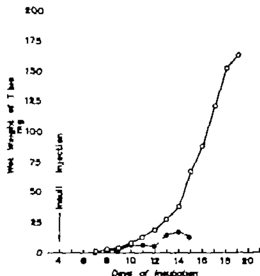


Fig. 3. Wet weight of tibia in insulin-injected (broken line) and control embryos (continuous line).

induced micromelic material. The main purpose of this investigation is to determine if there are any detectable differences in the chemical composition of the skeleton during normal and teratogenetic embryonic development

Methods and Material

An insulin solution was used containing 6 I.U or 0..5 mg I crystalline insulin per 0.05 ml of physiologic saline with acid pH (bout 4.3) A high insulin dose, 6 I.U were injected in the yolk sac of 770 eggs t the 4th day of incubation. Another 741 eggs which were not injected were used as controls. A high mortality was bserved in the injected series. Thus only 180 embryos, or bout 23 % survived the injection.

The incidence of micromelia has been registered by determinations f the length and the wet weight of the embryonic tibiae The occurrence of micromelia in the injected eggs was very high. In almost every case the tibia values of the injected series were lying below the averages of the controls of the same age The curves of the tibia length and wet weight were lower in the injected than in the control embryos (Figs. 2 and 3)

Malformations other than micromelia were also observed in some instances among the embryos f the injected series, such as clawfoot, beak deformities and recurvation of the tibia. Similar deformities were also observed in a few cases among the controls.

Quantitative determinations of the alkaline phosphatase activity were performed by the method of King & Armstrong [6] as modified by Sevastikoglou [14]. The whole tibia of the embryos was used for these estimations.

The collagen content f the tibiae was studied by quantitative determinations of their hydroxyproline content by the method of Neuman & Logan [12].

Results and Discussion

The enzymatic activity during the normal embryonic development was found to follow a more or less regularly rising curve In insulin injected embryos the evolution of the activity of this enzyme showed an irregular development (Fig 4) The spread

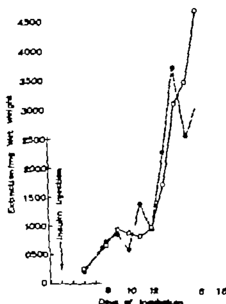


Fig 4 The alkaline phosphatase activity in tibiae of insulin-injected (broken line) and control embryos (continuous line)

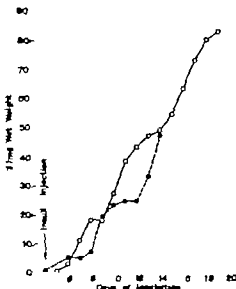


Fig. 5. The hydroxyproline content in tibiae of insulin-injected (broken line) and control embryos (continuous line).

ing of the values was wider than in the controls.

Both in injected and control embryos the hydroxyproline content of the tibiae rose progressively with the time of incubation and followed in both cases an almost parallel evolution. However the hydroxyproline content was always lower in insulin injected tibiae than in the controls (Fig 5)

The present investigation is still in a preliminary stage and any interpretation of the reported results must be guarded However it has been shown that both alkaline phosphatase activity and hydroxyproline content of the bones followed a different course during normal and teratogenetic embryonic development. Alkaline phosphatase has previously been considered to interfere with the calcification of the skeleton (Robison [13] and others) Recent work including that of the present author (Serastikoglou [14]) suggests that this enzyme is involved rather in the processes of bone differentiation. The irregular course of the activity of this enzyme under the prevailing experimental conditions might be explained as an irregular production of bone during the embryonic development in micromelia while at the same time the collagen content of the bones is lower than in normal embryos.

Summary

Six I.U or 0.25 mg crystalline insulin in 0 05 ml physiologic saline have been injected in the yolk sac of fertilized hens eggs at the 4th day of incubation. A high incidence of micromelia occurred and was registered by comparative studies of the length and the wet weight of the tibia at

different stages of the embryonic development in injected and control material.

The alkaline phosphatase activity of the tibia followed an irregular undulating rise during embryonic development in insulin injected material, while a regular rise of the enzymatic activity was observed in the control material. The hydroxyproline content of the tibia was lower in the injected embryos compared with the normals at the same stage of development.

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Orthopaedic Department
Akademiska Jukhuset
Uppsala
Sweden

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From the Pediatric Department of Flensburg Children Hospital, Malmö

The Frequency of Cystic Fibrosis of the Pancreas in Sweden

by PER SELANDER

Among the theories concerning the cause of pancreatic fibrosis the one based on a hereditary factor is generally accepted. Studies indicate the disease to be caused by a recessive gene [1 3 4, 5 6 8, 9].

The frequency of pancreatic fibrosis is stated to be 7 per 10 000 births in Switzerland [4], 1 to 10 in London [5], 7 to 10 in a larger region in the United States [6], 10 in Massachusetts [7], and 17 per 10 000 births in New York City [2 3] Thus the investigations indicate a frequency of approximately 5 to 10 per 10 000 with the exception of New York City where two to three times th frequency is reported. The figures from the United States are based on examinations of aut psy material and questionnaires to pediatricians. The resultant figures may be weighted insofar as the autopsy material constitutes a selection of children, and the reply to the questionnaires s more likely to be by doctors who have seen such cases than those who have not seen any Furthermore there is risk of multiple registration because several physicians may see a child with such a severe and prolonged disease The American figures may therefore be suspected of being somewhat too high The English frequency data re very pproximate The figures from Switzerland appear to be more representative More careful frequency studies are however desirable.

Present Investigation

There are 39 pediatric linics distributed throughout Sweden. This means that every severely sick child has access to a pediatrician. Therefore it is unlikely that any great number of children with pancreatic fibrosis would be overlooked. Thus, a tabulation of the diagnosed or suspected cases from the Swedish pediatric hospitals should yield as exact a picture of the occurrence of the disease in the country as is practically possible Mild and atypical forms that have been discovered during recent years [7] may not have been diagnosed in my material, but these have not been included either in the frequency figures from other countries

During the period 1950 to 1957 there were 870 032 live births in Sweden. Until December 31 1959 a verified diagnosis of pancreati fibrosis had been made in 92 of these children and it was suspected in 21 others Consequently the frequency of verified pancreatic fibrosis is 1.3 pe 10 000 (T bles 1 and 2) Although som of th children born during this period will prove to have the disease later on, one can

TABLE 1 *The number of live births in Sweden during the years 1950–1957 and the number of cases of verified or suspected pancreatic fibrosis among these.*

Year	Number of live births	Number of cases of pancreatic fibrosis up to 31/12/59	Frequency per 10,000
1950	114,726	10	0.9
1951	109,532	9	0.8
1952	109,523	15	1 4
1953	109,309	6	0.6
1954	104,943	21	2.0
1955	107 188	18	1.7
1956	107 773	17	1 6
1957	107 028	17	1.5
Total	870,032	113	1.3

TABLE 2 *The number of live births in Sweden during the years 1950–1957 and the number of cases of verified or suspected pancreatic fibrosis among these according to city and county*

City or county	Number of live births	Number of cases of pancreatic fibrosis up to 31/12/59	Frequency per 10,000
Stockholm	137 028	21	1.5
Göteborg [a]	47,377	4	0.8
Malmö	24,520	0	0
Norrköping [a]	13,026	5	3.8
Hälsingborg [a]	11 471	1	1 0
Uppsala	22,093	4	1.8
Södermanland	25,958	0	0
Östergötland	29,371	7	2.4
Jönköping	34 446	3	0.9
Kronoberg	18,190	2	1 1
Kalmar	26,536	1	0.4
Gotland	9,262	1	1.2
Blekinge	16,573	4	2.4
Kristianstad	30 738	11	3.5
Malmöhus	32,308	5	1.5
Halland	19 165	0	0
Göteborgs and Bohus län	32,328	0	0
Älvsborg	42,125	11	2.6
Skaraborg	29,960	4	1 1
Värmland	32,724	4	1.2
Örebro	27 970	4	1 4
Västmanland	27 431	3	1 1
Kopparberg	32,466	3	0.9
Gävleborg	34,382	0	0
Västernorrland	35,043	5	1 4
Jämtland	17 768	1	0 6
Västerbotten	31,987	4	1.2
Norrbotten	37,542	5	1.3
Total	870,032	113	1.3

City and county [a] City County: the remaining names in the list all refer to counties.

predict that the numbers will be small and will not materially effect the frequency figures. The basis for this prediction is that among the 146 cases of verified pancreatic fibrosis in Sweden 94% had significant symptoms before 2 years of age. Furthermore in a series from England more than 95% exhibited symptoms before 2 years of age [5], and in another series all had started before 16 months [8].

Discussion

The low frequency of pancreatic fibrosis in Sweden compared with that reported from other countries especially the United States is remarkable Considering the fact that the disease is rare in Negroes, Jews and Asiatics and that it occurs mainly among Europeans and their descendants [1 4 6 8 9 10], the frequency in New York City appears to be 15 to 20 times higher than in Sweden That a large number of cases were undiagnosed is contradicted by the fact that in the five largest Swedish cities, where diagnostic resources are readily available there was not a higher frequency in fact the incidence was the same as in the smaller towns and in rural districts. Even if the methods on which the American frequency figures are based can be criticised, it seems inescapable that there is a significant difference in frequency between Sweden and the United States and also between Sweden and Switzerland.

Summary

In Sweden during 1950 to 1957 the frequency of cystic fibrosis of the pancreas among 870 022 live births was 1 to 1.3 per 10 000 This is a low frequency compared with that reported from other places, especially the United States

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Pediatric Department
Flensburg Children Hospital
Malmö
Sweden

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(From the Pediatric Clinic, Karolinska Sjukhuset, Stockholm, Sweden)

Respiratory Studies in Children. IX

Relationships between Mechanical Properties of the Lungs Lung Volumes and Ventilatory Capacity in Healthy Children 7–15 Years of Age[1]

by INGA ENGSTRÖM, PETTER KARLBERG and CHARLES L. SWARTS[2]

The pulmonary function in children has attracted a great deal of interest in recent years as it has been found that methods which are used for studies in adults are also applicable in children. Although several studies on lung volumes and ventilatory capacity have been reported in healthy and asthmatic children [1 2 11 1– 17], the mechanics of breathing has not been as widely investigated. There exists abundant literature concerning the mechanics of breathing in adults, as well as a few studies in newborns. Of the studies in which children were included [3 17 20 25] the study of Helliesen *et al* [17] is the largest, *giving data of the mechanics of* breathing and the lung volumes in 77 healthy children 5–17 years of age The relationship between the mechanics of breathing and body size found both in healthy children [17] and adults [13] is not close enough to permit assessment of more than gross abnormalities The fact that a closer correlation has been found between lung compliance and vital capacity and functional residual capacity [17 20] has prompted us to determine if the relationships between different pulmonary functions may form a better basis for judgement of pathological lung function. For these reasons the mechanics of breathing, the lung volumes and the ventilatory capacity as judged from the forced timed vital capacity have been studied during the same study period in a group of healthy children. Normal values for each function are given for comparison with those previously reported and the relationships between different functions have been analyzed in an attempt to get improved tools for the investigation of lung function in asthmatic children.

Material

Forty five healthy children between the ages of 7 and 15 years, of whom 21 were boys and 24 girls, were studied. Most of the children were from a public school; a few children who were visiting the out patient department for minor diseases not affecting heart or lungs were also studied All the children were healthy regarding the cardiorespiratory system by history and gross examination. The children physical development was assessed by relating height to age and weight to height and all were within the 95 confidence intervals for normal Swedish children for these relationships [4].

[1] Aided by grant from the Swedish National Association against Heart and Chest Diseases

[2] 908 North Kenilworth, Oak Park, Ill., USA.

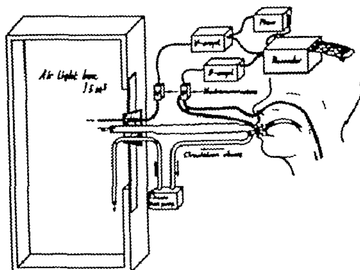


Fig. 1 Diagram of apparatus used for studies of the mechanics of breathing.

Methods

Mechanics of breathing

Simultaneous recording of changes in volume and changes in intraesophageal pressure allows separation of the elastic and the flow-resistive forces involved in breathing, thus enabling a calculation of lung compliance and pulmonary flow resistance. This principle of registration has been widely used since the studies of Buitendijk [8]. The technique of obtaining these data has varied however. The method used in this study is essentially the same as that described by Karlberg *et al.* for studies in newborns [19]. The tidal volume was recorded by having the child breathe into an airtight box of approximately 1500 liter volume which served as reverse plethysmograph (Fig. 1). The resultant pressure changes during breathing in the closed system were picked up by an electromanometer (strain gauge type Elema) then amplified and registered with a direct writing recorder (Mingograph 42, Elema). Before each recording the system was calibrated by pump with known stroke volume. The pressure changes caused by variation of volume within the system at usual tidal volumes were less than 0.3 cm H_2O. To avoid rebreathing in the tubes, a circulation shunt with a membrane pump which caused no interfering pressure fluctuations in the closed system, was connected from the mouth piece to the bottom of the box.

The signals from the volume electromanometer were also derived into flow rate by means of a specially constructed electronic device [10] and recorded on another channel of the recorder. The flow rate was calibrated from the slopes of simultaneously recorded volume curves at points of maximal flow obtained during calibration. All volumes were corrected to BTPS.

Changes in intraesophageal pressure have been used as an index of transpulmonary pressure changes, the intraesophageal pressure being considered as a sufficient approximation of the intrapleural pressure [6, 9, 21], at least in the tidal volume range observed in this study [7]. The intraesophageal pressure changes were recorded by means of an air filled (2 ml) latex balloon, 15 cm in length, sealed around a polyethylene catheter 1.5 cm in diameter connected to an electromanometer (Elema). The pressure changes were registered on a third channel of the direct writing recorder (see below).

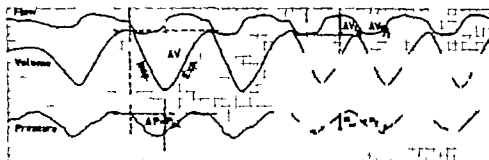


Fig — Mechanical properties of the lungs directly calculated from the record.
Compliance: V/P $_1$ ml/cm H O Pulmonary flow resistance: $P_{fr}/(V/t)$ cm H_2O/l/sec. Elastance: P_{el}/V cm H_2O/ml. Conductance: (V/t)/P_{fr} l/sec/cm H_2O

The catheter was introduced through the nose after spraying with a topical anesthetic (Novesin–Cyklosan[®]), and the balloon placed in mid-esophagus, a distance of 30 to 40 cm from the nostrils, depending upon the child's size The accuracy of this distance was checked by X ray in a few patients of various height

After introduction of the catheter the nose was closed by a clip and the child was connected to the "reverse plethysmograph" with a mouth piece which was freely suspended and which allowed the child to move somewhat. Studies were not begun for a few minutes to allow esophageal activity t diminish.

Dynamic lung compliance (C_L) was calculated in ml/cm H O as the ratio $\Delta V/\Delta P$ where ΔV is the tidal volume and ΔP is the corresponding intraesophageal pressure change, i.e. measured between points of no flow at the end of expiration and inspiration (Fig).

Pulmonary flow resistance (R) was calculated in cm H_2O/l/sec as the ratio $\Delta P/\Delta V/t$ where ΔP is the pressure difference corresponding to the total flow change ($\Delta V/t$) between points of equal volume [14].

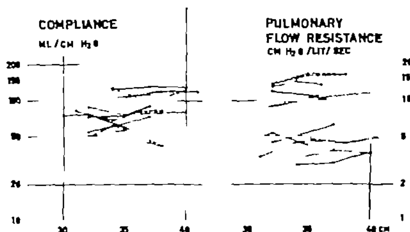


Fig 3. Lung compliance and pulmonary flow resistance in 11 children with two or three different catheter positions in each child. On the bscissa the distance between nostril and catheter tip.

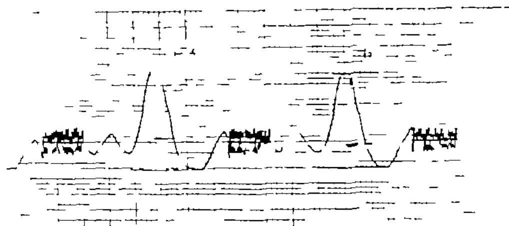


Fig. 4. A record of forced vital capacity with forced expiratory volume in one second.

giving an verage of inspiratory and ex piratory pulmonary flow resistance (Fig)

All measurements were made during quiet breathing over the range of normal tidal volume and frequency For all calcula tions two series of at least four even breaths with a constant end-expiratory level were used. The two breaths in the middle of each series were measured and calculated and the mean taken.

The most accurate way t use the intra-esophageal pressure as an index of trans-pulmonary pressure is to measure it against mouth pressure using differential electro-manometer In most of the children the intraesophageal pressure variations were measured against atmospheric pressure, because w did not have a differential electro-manometer at that time. This has been considered in the calculations: the slight pressure change in the closed system related to the tidal volume has been subtracted from the esophageal pressure in the compliance calculations and the flow resistance of the t bing in the system has been subtracted from the calculated flow resistance. T ascertain the accuracy f these corrections C_L and R have been measured in 25 children with and without a differential electromanometer After applying the corrections there is no significant difference between the two methods. (The mean percentage difference for C_L is -3.6 ± 3.6 and for R -0.04 ± 3.3.)

The influence of the position of the in traesophageal catheter has been tested by changing the position ± 3 cm from that used. There is no significant difference in C_L and R obtained at the different levels (Fig 3).

Static lung volumes

The closed circuit helium dil tion method with continuous addition of oxygen was used for determination of the functional residual capacity (V_{FRC}) The expiratory reserve volume (V_{ER}) and the inspiratory capacity (V_{IC}) were measured consecutively The residual volume (V_R) and the vital capacity (V_{VC}) were calculated from the data obtained. Doubl determinations were performed in each child. All volumes were corrected to BTPS. Details of the method and procedure have been previously described [11]

Since then few modifications of the ppa ratus have been made. The spirometer bell and the circulation pump have been exchanged, with the result that the fixed volume of the system is slightly increased (1.54 l instead of 1.46 l). The new circulation pump has capacity of 40–50 l/min. The spirometer bell is balanced according to the flow in the system, so that tmospheric pressure in the tube connections t the mouthpiece is established.

TABLE 1 *Random error of the method of determining compliance and pulmonary flow resistance.*

	Compliance $\Delta V/\Delta P$			Pulmonary flow resistance $\Delta P/\Delta V/t$		
	A	B	A+B	A	B	A+B
Number of double determinations	45	42	42	45	42	42
Mean difference ($\bar{d}$) liter	+2.5	+2.1	−1 05	+0.20	+0.28	+0.09
Standard deviation of the differences (σd) liter	±12.43	±11.36	±15.12	±1.58	±1.72	±1 45
Error in the mean differences ($\epsilon_{\bar{d}}$), liter	±2.00	±1 5	±2.32	±0.24	±0.27	±0.22
$t = \bar{d}/\epsilon_{\bar{d}}$	1.25	1 77	0.45	0.80	0.78	0 41
P	>0.1	0.1 > P > 0.05	>0.1	>0.1	>0.1	>0.1
Standard deviation in an individual determination (σx) liter	±9.5	±8.03	±10.70	±1 12	±1.22	±1.03
Mean of all double determinations ($\bar{x}$), liter	89.0	87 0	88.0	6.40	6.40	6.40
Coefficient of variation in a single det rmination (σx 100)/$\bar{x}$	±10.7 %	±9.2 %	±12.2 %	±17.5 %	±19.1 %	±17 7 %
Coefficient of variation in a duplicat determination (σx 100)/$\bar{x}$/$\sqrt{2}$	±7 6 %	±6.5 %	±8.6 %	±12.4 %	±13.5 %	±12.5 %

Forced vital capacity

The same spirometric system was used for determination of the forced vital capacity and the forced expiratory volume in one second (FEV $_{1.0}$) The kymograph of the spirometer was equipped with an electromagnetic gear allowing instantaneous shift in the speed to 12.5 mm/sec (constant within ±1 %) This enables a detailed analysis to be made of individual breaths. Four consecut ve maximal breaths with intervals of one minut were performed (Fig 4) The highest values of vital capacity and forced expiratory volume in one second, regardless of breath were chosen for calculation of the ratio FEV $_{1.0}$/V_{VC}. The volumes were corrected to BTPS The "resistance of this system is 1.. cm H_2O/l/sec

Procedure

The three tests were performed consecutively with the child in a comfortable sitting position. The whole procedure took about 1½ hours. All the children cooperated well

Random error of the methods

The random error of the method for determining lung compliance and pulmonary flow resistance has been calculated both from the differences between the middle two breaths in each of two series of four breaths and between the mean of the two couples (Table 1) The coefficient of variation is of bout the same order for calculations from two consecutive breaths as for the means of the two couples. This indicates that the principal source of the random error in the calculation is the pressure variations in single breaths, which is caused mainly by the interference of the heart beats on the pressure tracing The mean compliance and resistance from four individual breaths selected as described gives a coefficient of variation of 8.6% and 1..5% respectively

The random error of the method for determining lung volumes has been calculated from the difference between double tests (T ble 2) as described in a previous report [11]. In this a well a in our earlier study f

TABLE 2. *Random error of the method of determining lung volumes in healthy children*

	V_{FRC}	V_{VC}	$FEV_{1.0}$	$V_{VC\ forced}$
Number of double determinations	45	45	45	45
Mean difference ($\bar{d}$), liter	−0.074	−0.035	−0.034	−0.0004
Standard deviation of the differences (σd), liter	±0.106	±0.074	±0.151	±0.040
Error in the mean differences ( ), liter	±0.016	±0.011	±0.024	±0.006
$t = \bar{d}/$	4.63	3.18	1.45	0.07
P =	<0.01	<0.01	>0.05	>0.05
Standard deviation in an individual determination (σx) liter	±0.077	±0.05	±0.107	±0.028
Mean of all double determinations ($\bar{x}$) liter	1.36	2.66	2.24	2.74
Coefficient of variation in single determination (σx 100)/$\bar{x}$	±5.66%	±1.97%	±4.77%	±1.04%
Coefficient of variation in duplicate determination (σx 100) $\bar{x}/\sqrt{2}$	±3.99	±1.39	±3.37%	±0 4%

Mean of highest values.

healthy children, the functional residual capacity is statistically significantly lower in the second observation [11], due either to a real lowering of the end-expiratory level or to less absorption of helium in the blood during the second determination than during the first [18]. The coefficient of variation, however is only 3.99% in the mean of double determinations. The vital capacity is significantly larger in the second observation probably due to a training effect, but the coefficient of variation in the mean of double determinations is as low as 1.39%.

In calculation of the ratio of forced expiratory volume in one second to forced vital capacity the largest value of each volume has been used. In most children these values were measured from the same breath, although different breaths were used to obtain the largest values in some. The random error of the method has been calculated from the two largest sequential values of each volume. No statistically significant differences were found (Table 2).

The forced vital capacity in this study is significantly larger than the two-stage vital capacity (P 0.01), mainly due to the fact that the former is calculated from the largest value and the latter from the mean of double determinations. When the largest two-stage vital capacity is used for comparison, the significance disappears ($P > 0.05$).

Results

Because of the considerable range in size all values have been plotted versus height in double logarithmic scales as in previous studies [11, 12]. Figs. 5–7 show these relationships for compliance, resistance and $FEV_{1.0}$. Because all plots have a rectilinear relationship it was possible to perform regression calculations [23] on the various measurements of the lung function in relation to height (Table 3). All volumes are highly correlated to height. Lung compliance and pulmonary flow resistance have also been related to weight and sitting height (Table 3). There is a fairly good correlation to these body measurements but standard deviations around the line are larger than in the relations volume to height. All functions are related to about the third power of height. All have a positive correlation except pulmonary flow resistance which has a negative one.

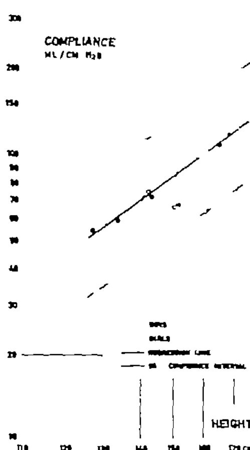


Fig. 5. Compliance in relation t body height on double logarithmic plot.

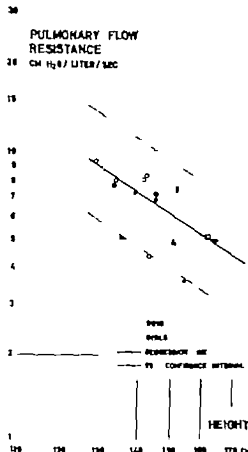


Fig 6. Pulmonary flow resistance in relation t height on double logarithmic plot.

The relationships between compliance and different lung volumes seem to be somewhat better than the relations to body measurements as indicated by the higher correlation coefficients (Table 3) One of these relationships is illustrated in Fig 8 The correlation between forced expiratory volume in one second and the inverse value of the pulmonary flow resistance (conductance in l/sec/cm H_2O) (Fig 9) is lower than between each of them to height as indicated by a lower correlation coefficient (Table 3)

The mean ratios V_R/V_{TLC}, V_{FRC}/V_{TLC} and $FEV_{1.0}/V_{VC}$ are tabulated below No significant correlation to height or age is found.

	Ratio	S D.
V_R/V_{TLC}	0 198	±0 031
V_{FRC}/V_{TLC}	0.403	±0 047
$FEV_{1.0}/V_{VC}$	0.820	±0.058

In Fig 10 V_{FRC}/V_{TLC} is plotted versus $FEV_{1.0}/V_{VC}$. A slight correlation appears to be present with a correlation coefficient of -0.337

TABLE 3 *Regression equations for lung volumes and mechanical factors of breathing with standard deviation and correlation coefficients*

Lung volumes in l, lung compliance (C_L) in ml/cm H_2O pulmonary flow resistance (R) in cm H_2O/l/sec conductance (cond.) in l/sec/cm H_2O height (H) and sitting height (SH) in cm, weight (W) in kg.

	Equation for the regression line y =	S.D around the line	
V_{FRC}/H	2.11 10 $H^{2.[illegible]}$	+16.7 −14.3	0.86[illegible]
V_R/H	1.00 10 $H^{2.13[illegible]}$	+19.1 −16.1%	0.837
V_{VC}/H	2.60 10 $H^{2.772}$	−1[illegible] −10.9	0.867
V_{TLC}/H	3.16 10[illegible] $H^{2.700}$	+11.2 −10.0	0.913
$FEV_{1.0}$/H	4.63 10^{-6} $H^{2.[illegible]}$	+1[illegible] 11.1	0.884
C_L/H	2.30 10[illegible] $H^{2.[illegible]}$	+20.0 11	0.727
C_L/W	1.71 $W^{1.071}$	+20.0 − 11	0.7 1
C_L/SH	3.13 $10^{-[illegible]}$ $SH^{3.[illegible]}$	+27.0 − 18	0.899
R/H	2.67 $10^{[illegible]}$ H [illegible]	+23.9 −19.3%	−0.728
R/W	1.24 10^{2} $W^{-0.[illegible]}$	+27.9 −21.8	−0.818
R SH	8 80 $10^{[illegible]}$ SH [illegible]	+27.6 −21.7%	−0.8 1
C_L/V_{FRC}	61.2 V + 4 [illegible]	±20.5 ml/cm H_2O	0.784
	8.906 $V^{0.[illegible]}$	+24.5 −19.7	0.773
C_L/V_R	122.9 V + 6.226	±18.9 ml/cm H_2O	0.813
	16.33 $V^{0.[illegible]}$	+22.6 −18.4%	0.808
C_L/V_{VC}	25.7 V − 6.962	±21.8 ml/cm H_2O	0.751
	2.80 $V^{1.[illegible]}$	+28.9 −19.3	0.786
C_L/V_{TLC}	30.4 V − 13 232	±19.5 ml/cm H_2O	0.800
	1.746 $V^{1.1[illegible]}$	+21 1 −17 4	0.812
$FEV_{1.0}$/cond.	6.16 cond. + 1.205	±0.458 ml	0.881
FEV /R	67.6 $R^{0.77[illegible]}$	+27.8 −21 6	−0.826

Discussion

The static lung volumes in this study have been measured with the same technique and procedure as in our earlier report on healthy children [11]. A comparison between the results shows a slight difference between the present and the previous values. The residual volume and the functional residual capacity are significantly lower in this study There is also an increase of total lung capacity but to a lesser degree For these reasons the mean V_R/V_{TLC} nd V_{FRC}/V_{TLC} are about lower in this study All differences, however are less than the standard deviations in a single determination and can be regarded as allowed variations in a method used over a 5 year period of time and with different technicians

The present lung volume data are in good agreement with other studies in healthy children reported during the last years [1 2, 17]

The method used for determining the timed vital capacity has given lower values of the ratio $FEV_{1.0}/V_{VC}$ than the method earlier described by us The mean value of 0 820 obtained in this study is significantly lower than the mean value of 0 850 in the previous study [1.] This must be due t the higher resistance in the

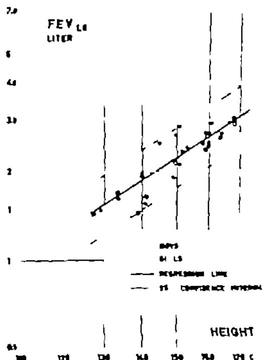


Fig. 7 Forced expiratory volume ($FEV_{1.0}$) in relation to height on a double logarithmic plot

spirometric system than in the box system used earlier However the variations in the ratio are somewhat lower in this study giving the same lower limit of the 95% confidence interval as before The present data are in good agreement with those reported by van Gelderen 0.822 using a similar technique [15] Bernstein *et al* [2] as well a Strang [24] however report slightly higher values of the ratio the former 0.86 and the latter 0.846 in boys and 0.886 in girls, probably also due to lower resistance in their spirometric systems

The lung compliance ha in this study as in others [13 17] shown a good correlation to body height Our data of compliance are also in good agreement with those reported by Helliesen *et al* [17].

It is an established fact that lung compliance is related to the size of the lungs as expressed in vital capacity and functional residual capacity [8 13 16 17 21 22]. Marshall s study [20] including 5 children and that of Helliesen *et al* [17] of 77 children are the only studies hitherto reported on children Marshall found the best correlation to functional residual capacity and Helliesen *et al* to vital capacity The present study has also given a good correlation between compliance and the different lung volumes. From the calculations the best correlation should be with the total lung capacity The correlation coefficients, however are of about the same magnitude and the advantage of one may be purely coincidental

As the calculated correlations apply to three different parameters, height compliance and lung volume it is possible that a relationship found between two may be indirect. To rule out any possible influence of that kind partial correlation calculations can be performed. Such calculations reveal that the correlation between compliance and height disappears when the lung volume is kept constant ($r\ C/H\ V_{VC}$ = 0 082) The correlation between compliance and the lung volume at constant height i reduced but still significant ($r\ C/V_{VC}\ H$ = 0 460) A high correlation between lung volume and height is still found at constant compliance ($r\ V_{VC}/H\ C$ = 0 778) (The same applies to all lung volumes) Thus, a direct relationship exists between lung compliance and lung volume irrespective of height whereas no true relation between lung compliance and height is found

Our values of pulmonary flow resistance are in good agreement with those of Helliesen *et al* although ours are somewhat

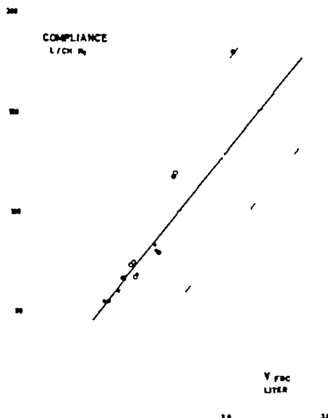


Fig. 8. Compliance in relation t functional residual capacity (V_{FRC}) Boys are marked with black dots and girls with open circles. The calculated regression line with 2 S D is drawn

higher but t the same time less varying The relation to height in our material is of about the same magnitude as that of compliance although it is an inverse rela tionship Th significant relationship probably depends upon the increase in size of the air passages during growth [11], giving a lesser pulmonary flow resistance a the air passages enlarge

There is reason to believe that the pul monary flow resistance should influence the forced xpiratory volume during one second presuming this volume being due not onl to the volume of ir in the lungs but also to the size and condition of the air passages. When relating these two values to each other a negative correlation is found, however less significant than between each of them to height. When testing these cor relations by partial correlation calculations there is still a correlation between forced expiratory volume nd height when resi stance is kept constant (FEV /H R = 0 601) and between resistance and height when forced expiratory vol me is kept constant (r R H FEV = −0 460) When height is kept consta t however no signi ficant correlation remains between forced

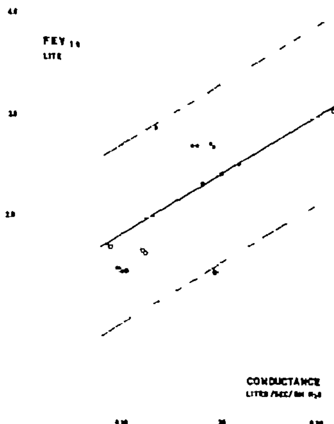


Fig. 9. Forced expiratory volume in one second ($FEV_{1.0}$) in relation t conductance. Boys are marked with black dots and girls with open circles. The calculated regression line with 2 S.D is drawn.

expiratory volume and resistance (r $FEV_{1.0}$/R H = −0.053) This lack of relation between forced expiratory volume and resistance in healthy children suggests that the former must primarily be a function of the size of the bellows, i.e. the vital capacity and not of the size of the air passages. This is also illustrated by the close correlation between forced expiratory volume and vital capacity irrespective of height (r $FEV_{1.0}/V_{VC}$ H = 0.733) and the lack of relation beetween forced expiratory volume and height at constant vital capacity (r $FEV_{1.0}$/H V_{VC} = 0.217)

In pathological conditions the relationships between lung compliance and lung volume may be changed and one of them cannot be used for prediction of the other but the relationships may be used as a pattern to which a pathological pulmonary function can be compared. The discrepancy between pulmonary flow resistance and forced expiratory volume during one second shows that these values are not interchangeable during normal conditions. Both are needed for a more thorough evaluation of the pulmonary function even if a correlation may arise during pathological conditions.

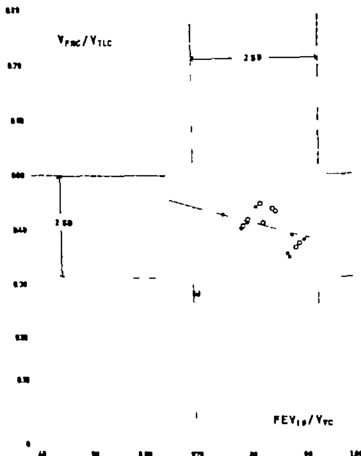


Fig. 10. The ratio of functional residual capacity to total lung capacity (V_{FRC}/V_{TLC}) in relation to the ratio of forced expiratory volume in one second to forced vital capacity ($FEV_{1.0}/V_{VC}$). Boys are marked with black dots and girls with open circles. The 95 % confidence intervals for both ratios are drawn. The calculated regression line for the combined ratios is drawn.

Summary

1 The mechanics of breathing the lung volumes and the forced vital capacity with the forced expiratory volume in 1 sec have been measured at the same study period in 45 healthy children from to 15 years

2. The relationships of these measurements to body size and to each other have been tested and the results are discussed.

3 Despite a relationship of some measurements no test has been found to serve as a substitute for another

4 A combination of all studies as described increases the precision for evaluating the pulmonary function.

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Pediatric Clinic
Karolinska Sjukhuset
Stockholm 60
S eden

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From the Department of Physiology II Karolinska Institutet Stockholm

On the Epileptogenic Properties of the Fetal Brain[1]

An Electrophysiological Study on the Electrically and Chemically Induced Convulsive Brain Activity in Sheep Fetuses

by C. G. BERNHARD I. H. KAISER[2] and G. M. KOLMODIN

Introduction

It is well known that children during the first year of life show a great susceptibility to convulsive disorders. Because of this, several investigations have been made of the sensitivity of the brain to seizure activity in *new-born animals* of various species [7 8 9 10 11]

Since on the basis of clinical observations it has been assumed that several factors may play a part in the development of convulsive disorders during the fetal period, an experimental analysis has been made of the epileptogenic properties of the brain during the *prenatal period*. This study was carried out on sheep fetuses in connection with an analysis of the development of the electrocorticogram in fetal sheep made in 1958 [5]. The cortical activity evoked by electrical and chemical (metrazol) stimulation in non-anaesthetized preparations was studied, and the results will be described in the present paper.

The gestation period of the sheep is, on an average 147 days, and the nervous system reaches a relatively high degree of maturation during the prenatal period (see e.g. Barcroft & Barron [7]). Thus when working on sheep fetuses kept in placental contact with decerebrat ewes, the ontogenetic development of cortical activity can be followed in non-anaesthetized preparations from early embryological stages up to a stage when the cortical functions are relatively well developed, as was shown in an earlier paper by Bernhard, Kaiser & Kolmodin [5]. In that study on fetuses with calculated ages from 65 to 151 days, a spontaneous cortical activity consisting of waxing and waning, temporary regional, spindle like bursts of regular waves (the PNI activity) was found as the only sign of activity up to about the 80th day of gestation. In later studies Bernhard & Kolmodin [6] found PNI activity present at a calculated fetal age of about 40 days. Around the 80th day an irregular activity (PNII activity) appears, and the compound cortical activity progressively becomes continuous and extended over the whole cortex.

Method

The ewe was decerebrated under the influence of thiogenal (methyl-thioethyl-2-pentyl thiobarbituric acid, sodium salt) a barbiturat which is rapidly eliminated. The fetus was delivered by caesarean section

[1] Supported by the Swedish Medical Research Council, Magnus Bergvalls Stiftelse, Stockholm and the Child Development Study of the University of Minnesota, U.S.A.

[2] Present address Department of Obstetrics and Gynecology School of Medicine University of Utah, Salt Lake City Utah.

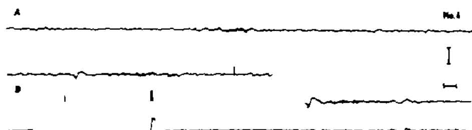


Fig. 1. Tracings in A show spontaneous cortical activity from two separate points in 200 g fetus (calculated age 78 days). Tracings in B the same as in A before and after repetitive cortical stimulation (marked by heavy line) during 6 seconds (stimulation frequency 25/sec). Horizontal bar 1 sec and vertical bar 200 µV

about one hour after the decerebration of the ewe. The head of the fetus was fixed in a stand, and after craniotomy the exposed brain was covered with paraffin oil (38°). Recording and stimulating electrodes were placed on the cortical surface. The cortical activity was recorded with a Grass electroencephalograph, and a Grass stimulator was used for electrical stimulation. The experiments usually started 2 hours after the injection of thiogenal, i.e. when the drug was eliminated; the recordings were thus performed on non-anesthetized preparations. In some preparations the fetus was immobilized with d-tubocurarine which was injected into a vein at a cotyledon. Control experiments were performed which showed that the d-tubocurarine did not change the reactivity of the fetal brain to metrazol and electrical stimulation. For further technical data and calculation of the fetal ages we refer to the paper by Bernhard, Kaiser & Kolmodin [5].

Results

The EEG in Fig. 1 A obtained from a fetus with a calculated age of 78 days shows the PN I activity which is typical of the early prenatal period (see above). Four fetuses belonging to this early prenatal period were tested and did not exhibit any epileptiform post-stimulatory after-discharge in response to electrical stimulation of the cortex even at high stimulus strengths (cf. Fig. 1 B and Table 1). As shown in Fig. 1 B a short burst of PN I activity appears 11 seconds after cessation of stimulation. This observation which was also made on the other fetuses belonging to this group indicates that the repetitive stimulation was not followed by any long lasting depressing effect on the PN I activity. Stimulations with high frequencies and long durations of the individual shocks (up to 5 msec) were also tested in these fetuses and were found to be without any effect.

As mentioned, an irregular spontaneous cortical activity (the PN II activity) appears around the 80–90th day and gradually both types of activity become continuous and extended over the cortex. Towards the end of the gestation period the PN II activity dominates the records (Fig. 2 A). In 13 out of 16 fetuses with calculated ages from 87 to 151 days and with corticograms exhibiting a PN II activity epileptiform after-discharge could be evoked by cortical stimulation (see Table 1). A typical example is illustrated in Fig. 2 B. In this experiment the epileptiform after-discharge has a duration of about 1[illegible] seconds and there is a synchronization of

TABLE 1 *Elicitation of epileptiform brain activity by metrazol and electrical cortical stimulation at different fetal ages*

+ = cortical response; − = no response.

Calculated age (days)	Type of spont. activity	Effect of metrazol (dosage 20–80 mg/kg)	Effect of el. stim.
63	PN I	Not tested	−
75	PN I	+	−
8	PN I	+	−
78	PN I	+	Not tested
86	PN I	+	−
87	PN I + PN II	+	−
97	PN I + PN II	Not tested	−
93	PN I + PN II	+	+
101	PN I + PN II	+	+
110	PN I + PN II	+	−
112	PN I + PN II	Not tested	+
11	PN I + PN II	Not tested	+
113	PN I + PN II	+	+
115	PN I + PN II	+	+
125	PN I + PN II	+	
128	PN I + PN II	+	−
129	PN I + PN II	Not tested	+
134	PN I + PN II		+
144	PN I + PN II	Not tested	
148	PN I + PN II	Not tested	−
151	PN I + PN II	Not tested	+

the rhythmical activity led off from the different cortical points. In most cases the epileptiform activity was obtained from the whole exposed part of the hemispheres, i.e. about two-thirds of the whole cortex, the extreme frontal and occipital part not being exposed. The youngest fetus in which post-stimulatory after-discharge could be elicited had a calculated age of 93 days. The three fetuses which did not exhibit any epileptiform after-discharge were of the ages 8‾ 97 and 110 days. The results obtained on this material did not indicate any significant difference



Fig. Tracings in *A* show spontaneous cortical activity from three separate cortical points in 100 g fetus (calculated age 125 days). Tracings in *B* the same as in *A* before and after repetitive cortical stimulation (marked by heavy line) during 6 seconds (stimulation frequency 25/sec). Horizontal bar 1 sec. and vertical bar ‾ μV.

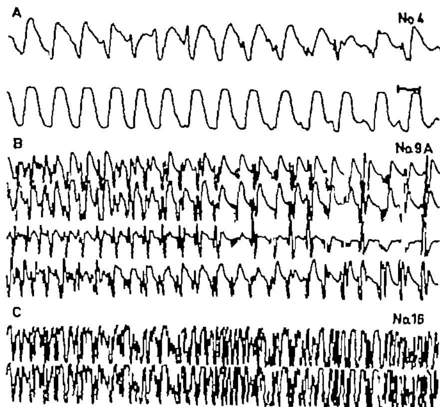


Fig. 3. Metrazol-induced epileptiform cortical activity. *A*, from same fetus as in Fig. 1 (calculated age 78 days). *B*, from 1300 g fetus (calculated age 128 days). *C*, from a 100 g fetus (calculated age 144 days). Horizontal bar 1 sec.

between the fetuses as regards the threshold at which the post-stimulatory after discharge could be evoked

In contrast to electrical stimulation the injection of metrazol evoked convulsive activity in all fetuses tested both in those of the early prenatal period characterized by the isolated PNI activity (4 fetuses) and those of the later prenatal period (0 fetuses). The records in Fig 3 illustrate the maximal effect obtained on three different fetuses just after the injection of metrazol. Fig 3 *A* illustrates the effect of 10 mg metrazol injected into a cotyledonary vessel of a 200 g fetus (calculated age 8 days) The metrazol induced activity consists of series of well-synchronized high voltage slow waves Fig 3 *B* and *C* show the metrazol effect in a 1300 g fetus (calculated age 128 days) and a 100 g fetus (calculated age 144 days) i.e. from fetuses at two different stages of the late prenatal period characterized by the spontaneous PNII activity In the older fetuses the injection evokes high voltage spike and wave complexes The records also demonstrate that there is a marked increase in discharge frequency with age Thus, the frequency of the metrazol induced activity is about 0 per second in the 78-day fetus and increases with age to about 2.5 per second in the 128-day fetus and 4.0

per second in the 144-day fetus Although a detailed analysis of the locus of these discharges was not made in all cases, it was *obvious that the observed effect is a* generalized activity spread over the whole cortex (cf Fig 3 *B*)

In most fetuses recordings were made from the sciatic nerve during electrical stimulation as well as during the convulsive state following electrical stimulation and metrazol injection. Efferent discharges in the nerve as a result of the convulsive brain activity were never seen in these experiments. Control experiments on non curarized preparations showed that no motor responses (i e tonic or clonic muscle activity) to cortical stimulation appear in sheep fetuses. Electrophysiological studies were also made on some spinal cord reflexes (cf later investigations by Änggård, Bergström & Bernhard [1]) and it was found that segmental reflexes could be elicited in several of the fetal preparations which did not show any motor reaction to cortical stimulation In the new born animal however electrical stimulation of the cortex was followed by *motor reactions.*

Discussion

Obviously metrazol induced *activity* consisting of high-volt ge slow waves can be evoked in the sheep during the prenatal period even at the early fetal st ge characterized by the PV I activity alone On the other hand, electrical cortical stimulation does not evok any post-stimulatory after-discharge until th cortical activity of the PV II type has appeared. Thus the fetal brain of the sheep is able to exhibit a repetitive synchronized activity before the cortex is electrically excitable as judged by the appearance of cortical post-stimulatory after-discharge

This suggests that functional connections necessary for an epileptiform discharge are developed rather early but that other factors which are necessary for an electrical induction of the epileptiform activity develop later In a study of the mode of action of electroconvulsive therapy in man Ottosson [12] found that intravenous lidocaine in anticonvulsive doses (Bernhard & Bohm [4]) changed the EEG pattern of the seizure by the reduction of the fast activity (spikes) so that slow waves of high voltage predominate. He suggests that since intravenous lidocaine in such doses has been assumed to affect ephaptic transmission [3], leaving synaptic transmission relatively unaffected, the slow waves may be of synaptic origin. Our findings that with increasing age the metrazol-induced activity changes from slow waves to spike and wa es or polyspike and wave complexes (Fig 3) might imply that the epileptiform discharges in the early fetal stages have a *synaptic background.*

It should be noted that descending spinal activity of enough effectiveness to evoke motor responses could not be ob*tained during the fetal life of this species* although th cortex is electrically excit able and the spinal reflex arcs are functionally active This fact may depend on the poor functional development of the descending systems in the sheep t the fetal stage Our observations that monosynaptic reflexes remain uninfluenced by conditioning cortical stimulation support this conclusion

When discussing the clinical aspects of

the results, one should stress the dangers of drawing too far reaching conclusions based on animal experiments. The brains of different species including man, devel op at different rates during the prenatal period, and the degree of maturation at birth is independent of the duration of the gestation period The observation that epileptiform cortical activity can be evoked by metrazol early during the pre natal period when the corticogram is characterized by PN I activity alone shows that epileptic brain activity may become evident in a functionally undifferentiated nervous system. On the basis of these results one is justified in assuming that convulsive brain activity may also exist in the human brain, which activity may cause damage to the fetal nervous system To our knowledge intra uterine epilepsy has however not been described in man.[1] In the experiments described above the cortical epileptiform discharges either chemically or electrically induced, were never followed by any motor activity Although one must bear in mind the possibility that during the prenatal period the influence upon the motoneurons from supraspinal levels may be less effective in sheep than in man these findings show that, if convulsive brain activity exists in the human fetus such activity may not necessarily be accompanied by any motor responses. The findings may thus help to explain why intrauterine epileptic fits have never been observed in humans

[1] While the paper was in press we have found a report by M. K. Badr El Din on A Familiar Convulsive Disorder with an Unusual Onset during Intrauterine Life in *J Pediat 56* 655, 1960.

Summary

The epileptiform cortical activity evoked by electrical and chemical (metrazol) stimulation was studied in non-anesthetized sheep fetuses kept in placental contact with the decerebrate ewe The investigations were performed on 21 fetuses with calculated ages from 65 to 151 days. It was found that electrical cortical stimulation did not evoke any post-stimulatory epileptiform cortical activity in the early prenatal period during which the electrocorticogram is characterized by spontaneous PN I activity alone (up to about the 87th day) In 13 fetuses out of 16 belonging to the following period characterized by PN II activity post-stimulatory epileptiform activity could be evoked On the other hand, metrazol activity consisting of high-amplitude potential waves could be evoked in all fetuses tested including both the younger ones exhibiting the PN I activity alone and the more mature ones showing a PN II activity The clinical implications of the results are discussed.

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Department of Physiology II
Karolinska Institutet
Solnavägen 1
Stockholm 60
Sweden

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CASE REPORT

Spontaneous Subluxation of the Atlanto-Axial Joint

by S BRÜNNER and H. ROVSING

From th Department of Radiology (Directors E. de Fine Licht and Oluf Petersen, M.D) and the Pediatric Department (Di ector P W Brandrup, M.D), Copenhagen County Hospital, Gentofte Denmark

Spontaneous subluxation of the atlanto-axial joint is defined as subluxation of the joints between the atlas and axis which occurs without a known or adequate trauma and furthermore is preceded in the great majority of cases by inflamma tion of the upper part of the neck, the face or the base of the skull. Disten sionsluxation" (Wittek) inflammatory dislocation (Fitzwilliams) maladie de Grisel or spontaneous hyperaemic dislocation (Watson-Jones) are some of the synonyms used in the literature

It is a comparatively rare condition and was described for the first time in 1830 by Bell whose case proved fatal [1]. Since then a few reports of single cases or small series have appeared. In 1940 Sul livan could collect only 52 cases from the literature [10]. To our knowledge the disease wa not described in Scandinavian literature until Werne [14] and Boje Hansen & Hansen [*] reported a few cases.

A case observed at the Copenhagen County Hospital in Gentofte is reported

Case Report

A one-yea -old girl, the second of children, was born following an uncomplica ted delivery although one month past term. Birth weight 3500 g Although her growth and development had been normal she had repeated colds, bronchitis, and pharyngitis with elevation of temperature t approx. 40°C These had been treated with antibi otics with gradual improvement on each occasion. At the age of 10 months she dev loped pneumonia followed by ot tis media

The child was admitted for the first time to the Paediatric Department fter pyrexia of 2–3 days duration. During the 4 hours prior to admission she had developed a w ak cough associated with rattling respirat ons and, later cyanosis of the lips. On the day of admission perioc lar swelling and conjunc t vitis w noted.

H acute stat improved in few days and wa interpreted as a catarrhal condit n partially allergic. It was then noticed that the patient would t with her head tilted toward the left shoulder and turned to the right When in the sitting position and trying to follow an object w th her eyes she would keep her hea l fixed and t rn her body

Physical examination d l not how any abnormal ty of the neck In particula there wa no suboccipital tenderness and the ternocleidomastoid muscles were normal The head wa maintained in a fixed position, but w th some force t could be rotated t ward the left The restriction of movement subsided within a f w lays, but the patient preferred holding her head tilted forward and slightly rotated to the right It w noticed that she had hypoplasia of the left face

Radiographic examination of the cervical spine showed the vertebrae to be of normal size. On lateral views there was a displacement of the anterior arch of the atlas upward in relation to the axis, the inferior surface *of the arch being on a level with the t p of* the odontoid process of the axis (Fig. 1). Repeat films 4–5 days later were unchanged. There did not seem to be any indication for treatment and the patient was discharged.

X ra 3 months after the first admission was unchanged (Fig. 2) but the views w th the head flexed showed the arch to have moved down a few mm over the upper margin of the odontoid process. Five months fter the first admission she was re-admitted with fever nd convulsions. Between the admissions she had several upper respiratory infections, but her parents had not noticed any abnormality of her neck. At the time of the second admission, the patient could *move her limbs freel* fter the convulsion but would not turn her head to the left nor flex it. Physical examination showed no abnormality.

Seven months later the lateral X y was improved with the lower margin of the



Fig. 1. Initial X ra. There is displacement of the atlas upward in relation t he xis. Not the under surface of the arch is on level with the ip of he odon oid process.



Fig. 2. Three months later. The arch has slid *few mm over* he upper margin of the odontoid process.



Fig. 3. T n mon hs af er he first X ray. The lower margin of he anterior arch is mm below he ip of he odo oid process, but not et normal anatomical pos ion.

arch 5 mm below the tip of the odontoid process, although not yet in the normal anatomical position (Fig. 3). During the interval the parents had noticed restricted motion of the cervical spine.

Discussion

Clinical features. Spontaneous subluxation of the atlanto-axial joint is usually characterized by pronounced torticollis without demonstrable changes in the sternocleidomastoid muscles. Since the condition occurs mainly in children and adolescents, it has been confused with congenital torticollis. The subluxation may be of three types: anterior unilateral, anterior bilateral, and posterior unilateral.

By far the most common type, anterior unilateral subluxation, is characterized by torticollis with rotation of the neck to the normal side, the head being tilted toward the affected side and at the same time flexed anteriorly so that it may be difficult for the patient to open his mouth. This position is very painful and is often rigidly maintained. In a few cases the shoulder on the affected side may be elevated. At times the voice has a nasal quality because of partial obliteration of the rhinopharynx, the anterior arch projecting and being sometimes palpable as a bulge in the posterior pharyngeal wall. It is characteristic that on lateral gazing the patient can freely rotate his head to the normal side, while on gazing to the affected side he has to turn his body.

Lateral and posterior to the subluxated joint there is distinct tenderness, and the spinous process of the axis is often palpable on the normal side of the midline, indicating counter-rotation of this vertebra (Sudek's sign).

In posterior unilateral subluxation the neck is rotated toward the affected side. Sudek's sign is positive on this side, and there is no bulge in the rhinopharynx.

Anterior bilateral dislocation should be suspected when the head is tilted forward with little or no mobility and no lateral rotation. In such instances a considerable bulge is palpable on the posterior pharyngeal wall.

Severe cases have sometimes been accompanied by neurological symptoms such as reflex disturbances, alterations in sensibility, pareses, and paraplegias. The disease has rarely caused death due to pressure by the odontoid process of the axis on the posterior arch of the atlas, resulting in cord injury.

Radiological diagnosis. The radiological diagnosis of this condition involves certain difficulties because special views are required to disclose a subluxation. In the usual anteroposterior view of the cervical spine the three uppermost vertebrae are hidden by the jaw, and the lateral films do not always reveal a subluxation.

Several factors must be considered in order to diagnose a possible subluxation. The first is the position of the head in relation to the atlas and axis (in lateral as well as a. p. views): normally, the space between the medial incisor teeth can be projected on a vertical line through the odontoid process of the axis. Secondly, the facets between the atlas and axis must be visualized quite distinctly and must be symmetrical. Thirdly, the spinous process of the axis must be in the midline. The lateral view must be exact, and close contact between the anterior arch and the anterior aspect of the odontoid process of the axis must be assured. In anteroposte-

rior views of the cervical spine taken with the mouth open the joint space between the atlas and axis is visible and a subluxation presents itself distinctly

Lateral views do not show any definite signs in mild cases, while in more advanced cases they show a distinctly increased distance between the anterior arch and the odontoid process. In young children subluxation is frequently represented only by elevation of the atlas, the lower margin of the anterior arch being on a level with the tip of the odontoid process. Often, the atlas is tilted backward, so that the spinous processes of the atlas and axis touch.

Treatment Three forms of treatment are usually recommended. (1) traction, continuous or discontinuous by Glisson s sling or Crutchfield s tongs imbedded in the skull, (2) manipulation of the cervical spine with or without anaesthesia and (3) open reduction and fixation.

The first two methods have been used with varying success, but in most cases the subluxation has been reduced. Open reduction is considered only in cases of increasing radiological dislocation or in threatened cord injury

Pathophysiology The pathophysiology of spontaneous subluxation is not known with certainty but nearly all the reported cases, including the present one have been preceded by acute or chronic inflammation of the upper part of the neck, face or base of the skull. Catarrhal conditions acute rheumatic fever influenza tonsillitis, otitis media mastoiditis retropharyngeal abscess scarlet fever and tuberculous adenitis are among the diseases underlying the spontaneous subluxation The present case was preceded by repeated attacks of tonsillitis with high fever but it is a characteristic feature that the site or nature of the inflammatory lesion does not influence the subluxation. The interval between the inflammation and the onset of clinical subluxation has ranged from one day up to several weeks [5 10 14].

Opinions of the mechanism are divided Jacobs suggested relaxation of the ligaments due to the influence of the toxins [6], while in Grisel s opinion the inflammation led to contracture of the deep suboccipital cervical muscles and thereby to subluxation [4] Swanberg [11] reporting a case following upon tonsillectomy believed that the transverse ligament of the atlas must have been avulsed. This theory has been rejected by Werne among others as it fails to explain the milder cases of subluxation. Watson–Jones [1], reporting 2 cases of spontaneous subluxation, believed that the mechanism was a rupture of the attachment of the transverse ligament to the *massae laterales atlantis* because of decalcification of the anterior arch. On radiographs he demonstrated absence of the arch which had recalcified on follow up examination 4 months later He based his theory on Greig's demonstration of decalcification in hyperemia sclerosis in cases of reduced blood supply Incidentally he believed that 7–10 days of hyperemia in the area surrounding the atlas was sufficient to cause decalcification severe enough for the attachment of the transverse ligament to rupture On these grounds, Watson–Jones warned against leaving a fixation bandage for longer than 10 weeks in order not to risk further decalcification To this Werne objected that clinically and radiologically definite cases of subluxation might occur

with only one day's interval between the inflammation and the onset of subluxation.

It is our opinion that Werne's suggestion based on studies on the movement in the atlanto-axial joint is the most likely [15]. He concluded that the range of movement in this joint, apart from the osseous contact between the anterior margin of the occipital foramen and the odontoid process, is restricted solely by the ligaments: that the range of retroflexion is arrested by the tectorial membrane and lateral flexion by the alar ligament with simultaneous rotation of the anterior surface of the axis in the same direction as the lateral flexion, the movement being arrested when both alar ligaments are extended. In subluxation the transverse ligament of the atlas is relaxed because of hyperemia; the degree of subluxation is determined by individual variations in the direction and length of the alar ligament.

Spontaneous subluxation is not restricted to the atlanto-axial joint. It may be seen also in other joints, and Jacobs and Sullivan, among others, have compared it with spontaneous dislocation of the hip in patients with typhoid fever.

The disease affects children and adolescents almost exclusively but a case in a 62-year-old patient has been reported. In a series of 28 patients Wilson found 86 % to be under 12 years of age [16], and among 56 cases collected from the literature and his own experience Sullivan found 77 % to be younger than 12 [10]. There is no sex difference.

The patient described in the present paper had spontaneous subluxation, presumably related to her frequent attacks of tonsillitis. The latter seems relevant because the signs of subluxation were aggravated in association with the febrile attacks and the possibility of trauma could be definitely ruled out. The findings do not permit any deduction regarding the mechanism.

Summary

A case of spontaneous subluxation of the atlanto-axial joint is reported and the symptomatology is reviewed. The role of radiography and the diagnostic criteria are discussed. Lastly, the pathophysiological theories are discussed in relation to the present case.

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Radiological Department
Copenhagen County Hospital in Gentofte
Hellerup
Denmark

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Family 2. The parents are first cousins. There have been three children of the marriage. No. 1, a girl born 1957, died when 9½ months old (Dronning Louises Børnehospital). Angiocardiography performed 1 month before death showed the shape and filling of the left atrium and the left ventricle to remain unchanged during systole and diastole. In addition, an elevated pressure was found in the right half of the circulation with considerable respiratory fluctuations. There was no left-to-right shunt. ECG (three standard leads) showed $T_{1,2}$ to be negative with small deflections in the first lead and depressed $S-T_{2,3}$. Glucose tolerance test was normal. Necropsy revealed endocardial fibroelastosis in the left atrium and ventricle. The left ventricle was moderately dilated and thickened, the ductus arteriosus barely permitted passage of a mm probe. There were no other cardiac deformities. The cardiac valves and vessels were normal. No. ., a girl, is said to be healthy but examination of her has been impossible. No. 3, a boy born 1960, died at 2 months of age. His nutritional progress was normal until 10 days before death when his health began to decline. Edema developed around the eyes, and later he had attacks of dyspnoea, once or twice accompanied by cyanosis. He died 1½ hours after admission to the Pediatric Department, Rigshospitalet. Necropsy showed the lungs and pericardium to be normal. The heart was slightly hypertrophic. Incisions in the myocardium revealed a white discoloration inferiorly in the anterior wall of the left ventricle but otherwise no changes. The atria, ostia, valves and coronary vessels were normal. Microscopy disclosed endocardial fibroelastosis of the left ventricle. In addition, perivascular fibrosis in the myocardium of the right ventricle as well as mild interstitial myocardial fibrosis of both ventricles was found.

Discussion

The incidence of endocardial fibroelastosis among children is unknown. Thomas et al. [1] among 10,000 autopsies found 20 cases. Of these eight were children. Unfortunately the number of infants among the 10 000 autopsied patients is not stated. Lambert & Vlad [6] found endocardial fibroelastosis in 2? of 3306 autopsied children. A total of 390 had congenital heart anomalies. It is therefore impossible to assess whether endocardial fibroelastosis occurs at the same frequency among siblings as other forms of congenital heart defects [10]. However the observation of endocardial fibroelastosis among siblings argues in favor of a hereditary factor in the etiology. Rosahn [11] states that endocardial fibroelastosis is associated with changes in the small arteries of the heart and in other parenchymatous organs, but such generalized changes have not been demonstrated by other writers. He discusses different etiological theories and concludes that the etiology is presumably one of an inherited, altered constitution due to a recessive gene. Andersen & Kelly [1] have studied the frequency of endocardial fibroelastosis in congenital malformations of the heart. They found that mechanical factors such as pressure and an abnormal intracardiac blood flow are important factors in the development of endocardial fibroelastosis and, further that oxygen deficiency seems to play an essential part. Oppenheim [9] has studied the correlation between coarctation of the aorta and endocardial fibroelastosis. Of 19 infants with coarctation 10 also had endocardial fibroelastosis. Accordingly hypertension alone does not seem to cause endocardial fibroelastosis. Oppenheim believes endocardial fibroelastosis to be a developmental defect in agreement with other congenital heart diseases. Kelly & Andersen [5] have investigated

cases with primary endocardial fibroelastosis, i.e. without other cardiac malformations. They claim that the affection is due to a familial, metabolic defect of the myocardium. The consequent weakening of the myocardium will secondarily give rise to endocardial fibroelastosis. Black-Schaffer & Turner [3] have demonstrated hyperplasia of the myocardium in cases with primary endocardial fibroelastosis. They take the hyperplasia to be a congenital defect which interferes with the working capacity of the myocardium. This will chiefly involve the left ventricle. The result will be a dilatation of the left ventricle and subsequently endocardial fibroelastosis, which is regarded as a compensatory response to the weakening of the myocardium. Lambert & Vlad [6] agree with Black-Schaffer & Turner in referring the basal affection to the myocardium. Lehndorff [7] likewise regards the myocardial dysplasia as the primary cause of the disease.

Conclusion

Primary endocardial fibroelastosis is presumably caused by a congenital defect of the myocardium. Its occurrence among siblings suggests that the disease is inheritable just like other forms of congenital heart defects. In that case it must be due to a recessive not sex linked gene.

Summary

Cases are reported of primary endocardial fibroelastosis in two siblings within each of two sibships. The conclusion is drawn on the basis of these cases as well as reports in the literature that the disease presumably may be caused by a hereditary recessive not sex linked defect of the myocardium.

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Department of Pediatrics
Sundby Hospital
Copenhagen
Denmark

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Meeting June 4 1960

Bernard Schlesinger (London) The course of Still's disease and results of steroid therapy

The age of onset compared with that of rheumatic fever is considerably earlier and the disease can often begin in infancy Still disease may be confined to many systems of the body before the joints are affected, so that at first the true diagnosis is often obscured.

Various types of fever can occur Often the pyrexia is high and irregular but sometimes it is relapsing in nature, rather like that seen in lymphadenoma (Pel Ebstein) The rash is characteristic and a help in recognising an obscure case. Rarely it is purpuric or may even cause gangrenous patches. Polymorphonuclear leucocytosis is a feature of the acute stage of the disease which can obviously lead to the mistaken diagnosis of septicaemia or purulent arthritis, when at first only one joint is affected. In severe cases leucocytosis may be followed at a later stage by pancytopenia with purpura, and leukaemia may be suspected until it is excluded by marrow puncture. With this turn of events the child condition deteriorates rapidly and death usually results.

The aetiology of the disease is still unknown but occasionally general or local trauma can be precipitating factor Lymphadenopathy is an acknowledged sign of rheumatoid activity but its distribution is not related to the main joints involved and is rather systemic reaction.

The arthritis can take several forms fleeting arthralgia, torticollis, mono-articular involvement, intermittent hydrathrosis, and crico-arytenoid joint inflammation, causing stridor and respiratory embarrassment. Pericarditis is a well known complication, arising either acutely or more often insidiously being only discovered at post mortem many years later Iridocyclitis is not very common, which is fortunate, as little can be done to prevent its progress. Other collagen diseases, such as dermatomyositis or scleroderma, are occasionally associated with Still's disease but the combination is uncommon.

Comparing the results of treatment, it has been found that steroids leave the least joint disability and encourage arrest of the disease. They may have to be continued for many months. Sixty three cases were thus treated and the results on the whole were very encouraging. Intra-articular prednisolone trimethylacetate has also been successfully employed when the knees are principally involved and moderate amount of fluid can be aspirated first.

There is little doubt that the ultimate prognosis has been substantially improved by steroids. They should therefore be used early and the lowest possible dose prescribed which will control any fever present and limit joint involvement as much as possible Children with Still disease have nature on their side and steroids are usually successful in preventing gross crippling by the time the disorder burns itself out spontaneously and relapses are no longer so likely to occur In this way the outlook is much more favourable in children than in adults.

Meeting October 10 1960

Helen B Taussig (Baltimore) Selection of cyanotic patients for operation.

In summary the patient who has a pulmonary stenosis and an intact ventricular septum should have a valvulotomy The indications for operation vary not with the age of the patient, but with the severity of the pulmonary stenosis. A young infant with great cardiac enlargement, clear lung fields and a pulsating liver should have a Potts transventricular valvulotomy In older children, progressive cardiac enlargement or electrocardiographic evidence of progressive right ventricular strain is an indication for operation.

Patients with pulmonary stenosis and a ventricular septal defect or an additional malformation should not have a valvulotomy without the correction of the underlying malformation. Infants may die of anoxaemia before the development of polycythaemia. Such infants should ha e a Potts anastomosis. The young children with a tetralogy of Fallot, with tricuspid atresia, with a single ventricle with pulmonary stenosis, and even some with a truncus arteriosus or a transposition of the great vessels with pulmonary stenosis suffer from polycythaemia and limitation of activity Such children may be greatly helped by a Blalock–Taussig operation. For older children, ten to twelve years of age, total correction is the ideal, provided the structure of the heart is such that it is possible; that is, they must have a pulmonary artery for the right ventricle and they must have not too great overriding of the aorta. It is highly desirable that there should be a pulmonary valve which can function and that the pulmonary arteries are of good size to take the entire circulation.

Inasmuch as more children can be helped by a Blalock Taussig operation than by total correction the clinical diagnosis should be rechecked before total correction is attempted. For older children in whom it is possible, total correction is the ideal and the results are extremely good.

Meeting December 5 1960

Mikko Hirvensalo Does the use of a mucus catheter increase infections in the newborn?

A study was made to find out whether the use of a mucus catheter in connection with ordinary resuscitation procedures does increase infections in newborns. The material comprises 102 newborns delivered at the old Institute of Midwifery in September–October 1959 Throat and nose swabs were taken at the beginning of the study from the midwives attending the deliveries. After they had completed suction of the nose and throat of the newly born a sample for bacterial culture was taken from the tip of the mucus catheter At the age of five days samples for culture were taken from the throat axilla and umbilicus of the infants. Skin infections were recorded too.

Results. Of the 102 infants investigated nine had *Staph. aureus* in the throat after resuscitation. Of these seven probably got it from the resuscitating midwife and two from the genital tract of the mother Of the 57 attending midwives 47% had *Staph aureus* in the throat or nose. As only 7% of the babies had *Staph. aureus* they are obviously not very likely to get infected during resuscitation. The frequency f skin infections was the same in infants who had been resuscitated by *Staph. aureus* carriers as in those resuscitated by non-carriers. The impression was gained that other sources of infection besides the one at resuscitation were of importance. Though it may be possible for the newborn to acquire pathogenic bacteria from the resuscitator via the mucus catheter the risk of infection from this seems rather minimal

Margett Kanas Experience in assessing the condition of newborns at the Institute of Midwifery

A material of 1033 infants born during a period of two months is presented. The Apgar scale of grading was used. If the estimate immediately after birth was 7 points or less, a new estimate was made 15 minutes after birth. The distribution of the infants into different categories according to their scoring was as follows (the latter score is used when two estimates were made): 9–10 points, 92.4 %, 7–8 points, 5.8 %, 4–6 points, 1.6 % and 1–3 points, 0.6 %. Eight (0.8 %) of the infants died; of these six scored between 1 to 6 points. A clear correlation could be observed between the score and maternal toxaemia, operative procedures during delivery and prematurity.

Meeting February 18 1961

Kari Penttinen. Viruses and the pediatric practitioner

Meeting April 5 1961

Charles A Janeway (Boston) The molecular basis of disease.

The rather grandiose title of this lecture refers to a conviction upon which the work of our own research group has been based, namely that since the many thousands of different protein molecules in the human body account for its anatomic form and for its living processes, disturbances in the structure or in the rates of production of specific protein molecules will account for most of the phenomena of disease. In other words, protein molecules are the basic biochemical units of the living organism, just as cells have been previously considered to be its basic anatomical units. We have worked on the plasma proteins, because with the development of methods for their isolation from human blood in a form suitable for clinical use by the late Professor Edwin J Cohn and his colleagues, they have become most readily available for physiologic and clinical studies. Our work has assumed that each plasma protein is a discrete entity with its own site of intracellular synthesis, its own metabolism and fate in the body and its own molecular structure adapted to performance of its particular function by interaction with small molecules and proteins in the blood and other tissues. It is our belief that knowledge of these properties for each of the plasma proteins will help us to understand normal physiological processes and should provide a starting point for the study of disease. In this lecture I should like to illustrate the application of the concepts by citing studies of two plasma proteins which are of particular interest to the pediatrician —*insulin*, a protein hormone and *gamma globulin*.

I *Insulin*

As an example of the contributions to medical knowledge which the protein chemist has been able to make, I should like to present recent studies on insulin by Dr Harry Antoniades Associate Investigator of the Protein Foundation, and his collaborators. Like many important discoveries, Dr Antoniades work was initiated by correct interpretation of the results of an experiment which seemed to fail. In trying to isolate insulin from blood plasma he found that the insulin activity which was detectable in the donor blood, could not be recovered in any of its fractions. It was apparently trapped in the cationic exchange resin used to remove calcium so as to prevent coagulation, but could not be eluted. In contrast radioactive insulin, added to plasma before passage over such a resin, was readily re

covered in the effluent. Thus exogenous in sulin did not behave like native insulin. Dr Antoniades reasoned that perhaps native insulin was bound to another protein for which the resin had a high affinity possibly due to its strongly basic character This in genious hypothesis was soon strengthened by other observations. (1) Insulin assays of fasting blood plasma, using muscle tissue, gave very low values for insulin activity while assays using adipose tissue gave much higher values. (2) Insulin could be recovered from the resin columns over which blood had been passed if the pH were raised to 10 On the basis of these observations Dr Antonia des postulated that insulin circulated as a complex with a basic protein, and that in this complex it was physiologically inactive Possibly adipose tissue contained an enzyme capable of splitting this complex, while muscle tissue did not.

This hypothesis was brilliantly confirmed by the demonstration first, that treatment of blood plasma with an extract of adipose tissue would indeed increase its insulin ac tivity markedly when assayed by the muscle tissue method, and second, that a highly basic protein could in fact be concentrated from human blood plasma.

Having demonstrated the existence of such a basic protein–insulin complex in blood, and subsequently in pancreas, Dr Antoniades and his collaborators turned their attention to the question of how the existence of this physiologically inactive complex might affect the metabolism of glucose in man. Elevation of the blood sugar as in a glucose tolerance test in normal per sons, was found to raise the level of circulating free (active) insulin and to lower the level of circulating protein bound insulin marked ly without affecting the total circulating insulin (bound plus free insulin) as deter mined by the adipose tissue assay When adult diabetic patients were studied in the same way they were found to have relatively normal fasting total insulin levels, with most of this insulin in the bound form, but when the blood sugar was raised, there was only a very slow liberation of free from bound insulin. *This suggests* very *strongly* that diabetes, in the adult at least, is not so much due to a deficiency of insulin as to an inabi lity to liberate insulin from the complex in which it normally circulates. Much remains to be done but these studies have certainly opened up exciting new lines of investiga tion for the student of human diabetes, which may change many of our ideas about the pathogenesis and treatment of this im portant disease.

II. *Gamma globulin*

The studies upon gamma globulin, or more properly the gamma globulins, are primarily those of Dr David Gitlin of our department and his associates, Dr Fred Rosen, Dr Walter Hitzig, and Dr John Craig The most difficult problem is to define this group of proteins. Although they share the slow range of electrophoretic mobilities from which their name is derived, upon ul tracentrifugation they can be separated into globulins with a sedimentation constant of 7 (7S or γ_2-globulins) and globulins with a much higher molecular weight, giving sedimentation constant of 19 (19S B_2 or γ macroglobulins). Upon immunoelectrophoresis, the technique developed by Grabar these proteins can be shown to include at least 5 immunologically distinct components.

A. *Source*. There is a great deal of evidence to indicate that 7S γ-globulins, the usual immune antibodies, are formed in lymphoid follicles in cells which ultimately assume the plasma cell morphology Included in this evidence is direct demonstration of the presence of diphtheria antitoxin in plasma cells of specifically stimulated, human lymph nodes and the absence of plasma cells from the poorly organized, lymphoid tissues of patients with agammaglobulinemia (the antibody-deficiency syndrome) The site of synthesis of the 19S, B_2 or γ-globulins is not clearly determined, but is obviously different

B. *Metabolism* The size of the body pool of the gamma globulins may change mark edly without hemodynamic disturbances because of the very slight osmotic activity

of these proteins, due to their low net charge. The half life of 7S gamma globulins in man appears to be in the order of 20–30 days.

C. *Disturbances in disease. Hypergammaglobulinemia* or an increased body pool of gamma globulins, occurs in a number of conditions, notably hepatic disease, the collagen diseases, chronic infections, or in the myelomas. Deficiency of gamma globulins or *hypogammaglobulinemia*, reflecting a decreased body pool may be the result either of decreased synthesis or of increased catabolism. The nephrotic syndrome is an example of the latter; the combination of urinary protein loss and increased catabolism, as revealed by studies with labeled proteins, results often in such a marked deficiency of antibody in the body fluids that increased susceptibility to invasive bacterial infection occurs. However most forms of the antibody-deficiency syndrome are due to a decreased rate of synthesis of antibody as shown by: (1) very low levels of circulating gamma globulins; (2) absence of plasma cells; (3) failure to form detectable antibodies after infection or immunization, (4) a normal or prolonged half-life of injected gamma globulins indicating a normal or decreased rate of catabolism. Where the deficiency is due to deficient gamma globulin synthesis, substitution therapy with regular injections of gamma globulin in large doses will be quite effective in protecting agammaglobulinemic patients from infection (0.1 g/kg will raise the level of circulating gamma globulin by 100 mg%, hence monthly injections of 0.1 g/kg are recommended once a loading dose of 0.2–0.3 g/kg has been given). In cases of hypercatabolic hypogammaglobulinemia, as in nephrosis, this type of therapy is of little benefit.

There are a number of different types of hypogammaglobulinemia due to failure of antibody synthesis which may result in the antibody deficiency syndrome—

I. Transient physiological hypogammaglobulinemia of early infancy

II. Congenital agammaglobulinemia

(a) Sex-linked recessive (usual type in boys)

(b) ? Autosomal recessive (rare cases in girls)

(c) Deficiency of B_2-M globulins with normal γ_1-globulins

III. Acquired "agammaglobulinemia" (both sexes)

(a) Destruction of lymphoid tissues by tumors, drugs, or X ray

(b) Idiopathic deficiency of plasma cells

(c) Severe protein malnutrition (?)

IV. Specific "immunological paralysis"

Some very interesting clinical observations have been made in gammaglobulinemic patients. Good had the opportunity to follow from birth the normal infant of a mother with acquired agammaglobulinemia and the congenitally agammaglobulinemic infant of a carrier mother. The first infant was born with no gamma globulins, but gamma globulins and typhoid agglutinin (typhoid immunization was started immediately after birth) began to appear after about 6–7 weeks of age and soon reached normally expected levels. The second infant was born with a normal level of gamma globulin which gradually fell to undetectable levels over a 6–8 month period. A surprisingly high incidence of collagen disease has been observed in agammaglobulinemic patients—principally a chronic arthritis, probably rheumatoid arthritis but also dermatomyositis and scleroderma. Recently we have had occasion to observe the development and disappearance of severe autoimmune disease in a boy of 18 with congenital agammaglobulinemia. Hemolytic anemia, leukopenia, thrombocytopenia and renal failure developed rapidly and were found to be associated with a high level of Forssmann antibody and an appreciable amount of 19S B_2 or γ_1-macroglobulins in the blood. The clinical disease and the macroglobulinemia subsided after splenectomy. In another patient without clinical manifestations, similar high levels of γ macroglobulins were found in the serum. These findings in two patients with very severe deficiency of 8 γ-globulins strongly suggest different sites of synthesis for the γ-macroglobulins and the 8 γ_2-globulins.

Here again studies of disturbed metabolism of specific plasma protein molecules have been helpful, not only in understanding the manifestations of disease in certain patients but in leading to the use of rational forms of therapy

Meeting May 10 1961

C. E. Räihä The influence of prenatal and natal factors on the development and diseases of the child.

J Kauhtio On the prognosis of epilepsy
Marianne Paatela. On microdissection of the kidney in congenital nephrosis.

K. Kouvalainen Immunological studies in congenital nephrosis.

L. Hjelt Influenza during pregnancy

Will be published in the Proceedings of the XIII Northern Pediatric Congress (*Acta Pædiat (Stockh.) Suppl.*, 1962).

Ilmari Kantero Helsinki

Norwegian Pediatric Society

Meeting Sept. 23, 1960

O Knutrud On treatment f Wilms tumor (nephroblastoma)

A composite material comprising 77 patients treated in Norway from 1942 up to and including 1957 is presented. This material has been followed up, and the histologic preparations have been reexamined by Professor Kreyberg Ten patients had to be left out because of insufficient information, which leaves a total material of 67 patients, of whom ten survived The period of survival ranged from two and a half to seventeen years. The material has been analysed and is compared with Gross s material from Boston and with a material from Great Ormond Street, London (Bodian) In the total Norwegian material the survival rate is 14.9 per cent, in patients treated in the first year of life, 30 per cent. Various methods of treatment have been used, which seems natural enough, seeing that the patients were treated in 33 different hospitals. However segregation of the patient treated by operation and radiation according to the Boston technique reveals that in this group the survival rate is 42 per cent. This tallies surprisingly well with the findings of Bodian and Gross who, in following the same technique, found a survival rate of 45 per cent and 47.2 per cent respectively In the Great Ormond Street series from 1925 up to and including 1948, 57 patients were treated with a quite undifferentiated technique with a survival rate of 12 per cent The same form of treatment was employed in Gross 1914–30 series giving a survival rat of 14.9 per cent. These rates correspond perfectly to the Norwegian rate of 14.9 per cent for patients given undifferentiated treatment. Thus, systematization of the treatment and improvement of the surgical technique cause the *survival rate to rise threefold*. The conformity of the results derived from three different materials in three different countries can hardly be fortuitous. It is apparent from the Norwegian material that the survival rate is no different in patients who have received roentgen therapy postoperatively and in patients that have not always assuming that both groups have been operated on by the Boston technique. From this can be drawn the inference that the chief factor is the surgical technique. It also clearly ppears that the patient should be treated immediately the diagnosis has been made i.e. as soon as the tumor has been palpated.

The survival rate is twice as high in the group that has been treated during the first week after admittance to hospital as in patients not treated until later. Preoperative roentgen treatment is not recommended because it retards operation, and also because there have been cases where tumor doses have been administered to patients with abdominal tumors which have later proved to be cystic kidneys etc. The survival rate is moreover far lower in the preoperatively treated group, as is also apparent from the other series. Immediate operation has not increased the fatality rate whereas, on the other hand, the preoperative roentgen therapy which has hoped to engender less dangerous surgical intervention has increased the mortality to a considerable extent. This is evident from all three materials. Professor Kreyberg has reexamined most of the preparations on which the diagnosis in the Norwegian material has been founded to ensure equal assessment, on the one hand, and to ascertain whether it is possible to draw conclusions as to prognosis from the histologic picture on the other. Without knowledge of the patient clinical record or the postoperative course Professor Kreyberg picked out three tumors so highly differentiated as to warrant special classification. Two of these patients are among the survivors. It is concluded that results are primarily dependent on immediate treatment and on cautious and proper surgical technique. As a consequence treatment of these patients should be centralized in order that some doctors be experienced in the procedure.

Haakon Kjeldsberg: Congenital skin and bone defect in the parietal area

The patient is girl born in January 1960 of healthy parents. Birth weight 2390 g. Height 49 cm. She had skin and bone defects measuring about 12 cm by 5 cm situated in the sagittal line between the fontanelles. The dura mater was completely exposed in the bottom of the defect. Conservative treatment gradually resulted in formation of granulation tissue which purified itself and filled the defect. By and by this was covered by skin growing in from the edges, so that when the child was discharged from hospital she had only small incrusted scalp wound. At about three weeks of age the patient had to have blood transfusions because of life-threatening bleeding from the wound edges. Cerebral complications were not observed. Follow-up examinations in the Out Patients Department have shown the patient psychomotor development to be normal. Whether the bone defect has been reduced is uncertain. Neuro-surgical treatment may be required later on.

Peter Johan Moe: Internal carotid thrombosis

Internal carotid thrombosis occurs frequently in adults, but is a rare condition in children. In children the most common causes are throat trauma, cardiac diseases, and local processes. A few cases of spontaneously occurring internal carotid thrombosis without known cause in children are mentioned in previous publications. The symptoms may vary considerably but the most characteristic symptom is hemiplegia of the contralateral side associated with reduced sensitivity to touch and pricks. In some cases palpation has revealed reduced or suspended pulsation in the affected carotid. The diagnosis can be confirmed by carotid angiography. A simple way of verifying the diagnosis is to measure the pressure by ophthalmodynamometer. For patients who survive the acute phase the prognosis seems good, more or less regardless of therapy. In the surviving patients complete restitution usually occurs in the course of about 6 months.

Case: S.L. is a 9-year-old girl who was admitted to the Pediatric Department, Oslo University Hospital, in June 1960 because of acute complete left-sided hemiplegia associated with loss of sensibility. Some days previously she had been feverish (throat infection?) Pulsation in the internal carotid was good on both sides. Conditions in the throat normal. Spinal fluid normal. Roentgenogram of the cranium and sinuses showed

nothing pathologic. The EEG revealed signs of lesions of the right hemisphere. Right-side carotid angiography disclosed contrast filling of the external carotid and branches. Left-side carotid angiography showed that the thrombosis extends from above the internal carotid's branching point on the right side. The patient has been on "Trombantin" for several months, and the adjustment has been easy After about a month some functional improvement was demonstrable. She is now able to walk quite well, but he function of her left hand is still poor

Sverre Halvorsen and Kjell Aas Renal tubular defects in fibrous dysplasia f the bones

In the Pediatric Department, Oslo University Hospital, we have had two patients with fibrous dysplasia of the bones and symptoms of renal tubular defects. The first patient, G.B presents a typical McCune–Albright syndrome associated with vitamin D resistant rickets. Continuous treatment with large doses of vitamin D has cured the rickets. In vitamin D resistant rickets a marked hyperphosphaturia is present. Fanconi & Girardet saw this as a primary tubular defect, whereas Albright and coworkers at an earlier date had maintained that the hyperphosphaturia is secondary to hyperparathyroidism caused by inadequate resorption of calcium from the intestine. Investigations in recent years have supported the theory that hyperphosphaturia by itself is not the cause of the vitamin D resistant rickets, but that a more general metabolic disturbance associated with tubular dysfunction is present. The second patient, N.S. has renal glycosuria in addition to the fibrous dysplasia of the bones. Her glycose tolerance is normal and the urine contains glycose under fast too This patient moreover has renal aminoaciduria. The combination of renal glycosuria and aminoaciduria has been described by Luder and Sheldon in four patients, representing three generations of the same family The aminoacid pattern in our patient corresponds to that described by these authors. As reabsorption of glycose, phosphates and amino acids takes place in the proximal tubules, we are able to place the defect in this part of the nephron in both our cases. The tubular defect is considered as a parallel anomaly

Meeting Oct. 28 1960

R. Lagercrantz (by invitation) Ulcerative colitis in children and adolescents

In the course f the last few decades ulcerative colitis in children has become more common in Sweden. About 100 patients with this condition have been treated in the Pediatric Department of Karolinska sjukhuset during the past few years. In many cases Broberger & Perlmann have demonstrated signs of autoimmunization against antigen from the mucous membrane of the colon. Thi gives an interesting angle t the diverse extracolonic symptoms of hypersensitive type (like erythema nodosum, arthralgia, erythrocyturia and certain liver injuries) that bout half of our patients present.

The onset is usually gradual with increasing diarrhea and emaciation, but cases with an acute, fulminating onset have become more frequent of late. Rectoscopy and radiographic examination (particularly of the rectum) are valuable diagnostic means, but in the early stages they do not always give conclusive findings. The course of the illness varies considerably In a previous series about 14 per cent of our patients died. The prognosis is much better now however thanks t improved therapeutic measures. About one-third of the patients in the present series have been free of symptoms, t any rate subjectively on follow up examination. Somewhat more than half of them presented more or less chronic, and more or less severe

symptoms. Most were retarded in their emotional development and about 5 per cent showed physical retardation too, for in stance, in the form of delayed puberty The longer the patient has had his disease the greater is the risk of developing cancer of the colon. In the twenty four patients who had had the disease for more than 15 years cancer of the colon occurred in 8 cases, and 7 of these patients died within the year

The treatment is individual As far as the disease allows, we have voided treating these patients as invalids. Most of them have received ambulant treatment and have been going to school or t work. They have been encouraged t tak part in pastime occupations t such extent as they felt up to In most cases the patients could eat normal, varied food in addition to which they were given salazopyrin, frequently for long time. This drug often had good effect on the symptoms. In acut cases and in cases where results were unsatisfactory we have em ployed adrenal cortical steroids or compound of similar effect. This treatment usually brought remission. However it has not been possible to prevent relapse and the result of renewed treatment have often been un satisfactory Local treatment has been beneficial, particularly in the subacut cases.

In recent years we have operated on pa tient whose lif wa threatened by toxic disease with or without perforation, and patient who in spit f medicinal treatment had not recovered satisfactorily Twenty three patient (17 per cent) ha e been treated with colectomy Ileo-rectal anastomosis was performed in 10 cases, ileostomy in 13. Result have been very good in that all patient have recovered.

DISCUSSION

Hjalmar Wergeland In lcerative colitis the significance of the psychic factors, etiologicall as well as pathogenetically seems to be surrounded with the same un certaint as are the somatic factors. Most psychiatrists seem t agree that in all pa tients there are signs of serious psychic conflicts, and that it is possible in most cases to prove that these were present before the first symptoms appeared. But with regard to the nature of these conflicts opi nions differ Fear of losing contact with someone dear seems quit common, also marked inhibition of all aggressiveness. In the two patients at the moment being treated in the Children Psychiatric Department of Oslo University Hospital this lack of ag gression is very pronounced. As long the etiology remains vague it will not be possible to institut causal treatment On the other hand, it is reasonable in such grave disorder to try everything that might be helpful, and one form or another of psychotherapy ought to be given a chance in ad dition to the usual medicinal treatment A question that is apt t arise is, for how long should such treatment be kept up before operation is considered? Good result of operation are frequently reported in medical publications; on the other hand, reports of relapse of the disease in the ileum following colectomy are not t all infrequent. The risk of this seems particularly gra in cases where the patient are relatively free of symptoms during change of environment as, for instance during hospitalization, but have relapses as soon as they get back t their homes. This is the case as regards our two patients One patient has been operated on but will not be discharged from the hospital until measures to solve the serious con flicts in her home have been taken. In the meanwhile the patient receive psychotherapy The second patient is relatively free of symptoms in periods, but develops diarrhea and bleeding if exposed t psychic stress, as, for instance when she goes home on vaca tions. Her home is too far way for effective help with the family problems to be practicable. Should she be operated upon? For the time being t has been decided to keep her in the hospital until w see what will happen to the operated patient once he is reestablished in her home

Bjarne Frethe m When indication for surgical treatment of ulcerative colitis is present the standard treatment in recent

years has been ileostomy and total colectomy With regard to indications the following criteria are used: signs of mortal danger as in fulminant toxemia, massive hemorrhage or perforation, serious disablement such as debility recto-vaginal fistula, ulcerations and arthritic changes. A chronic ulcerative colitis that has lasted for 3 years or more with relapses and extensive changes in the colon should probably be treated surgically In more acut cases operation at an even earlier date is recommended. It has been particularly difficult to decide on surgical treatment in children However since Aylett reported his cases of colectomy with ileo-rectal anastomosis in London in 1956 it has become a little easier to take the decision. The discomforts of frequent stools have not been as great as expected, 5 stools a day has been the average, and so far the clinical result look promising Up till now I have used this surgical procedure on two 10-year-old girls and on one 14 year-old boy in a one-stage operation in all cases. One of the girls, whose condition was far advanced, had local treatment of the rectum stump with hydrocortisone for a while. The two girls are in good health with loosely formed stools 5–8 times a day The boy is newly operated on. The rectal changes must evidently not be too pronounced at the time of operation, in particular strictures or fistulae must not be present. In case of relapse local treatment of the small rectum stump or establishment of abdominal ileostomy is possible

H J Ustvedt An epidemiologic study on ulcerative colitis in Norway especially in point of rat and age and sex distribution, published in Oxford in 1958 was briefly reported. The 451 cases, distributed over the decade 1946–55 showed marked rise of incidence from calendar year t calendar year In Medical Department B of Oslo University Hospital we have the impression that the rat of hospitalization has increased even more in the course of th past five years. Geographically speaking there were no differences in incidence within Norway On the other hand, comparison with Melrose study revealed a marked difference in incidence between Norway as a whole and England and Wales. A striking thing in the 1946–55 study is the *exceedingly low rates* for ulcerative colitis in childhood A rough comparison with rates from Stockholm, Uppsala, Lund and Gothenburg showed the hospitalization rat of ulcerative colitis to be 6–7 times as high in the Swedish towns as in Oslo and Bergen. Sources of error were pointed out. The desirability of a new joint Swedish Norwegian investigation was emphasized Proofs of the importance of psychic factors in the etiology are: observations on patients with fistulae, reports of psychotherapeutic results, the conspicuous influence of psychic conditions a provocative factor for relapse, and various clinical, psychologic and psychiatric observations It is pointed out that etiology and pathogenesis must not be confused. Autoimmunization cannot represent an etiologic mechanism, but might represent a pathogenetic one. In Medical Department B we prefer local steroid therapy (hydrocortisone enema) to peroral steriod treatment, because the former entails less risk of complications. Doctor Lagercrantz long-term observation as regards the frequency of cancer argues strongly in favour of surgical treatment f ulcerative colitis as cancer prophylaxis. In particular it should be noted that cancer may occur even when the patient has presented few and mild symptoms for a long period.

Karl W W fring Hemorrhagic tendency in newborn infants in connection with prophylactic vitamin K *treatment*

As in patients treated with anticoagulants the blood of newborn infant has a reduced content of the coagulant factors II (prothrombin) VII (proconvertin) IX (PTC), and X (Stuart Power). Vitamin K does not bring the content to adult values which are not reached till after some weeks. In newborn infants with hemorrhagic disease the content of these four factors is very much reduced and vitamin K brings values to the level that seems normal for newborns. By means of the

thrombotest method, which takes account of all the four coagulant factors that are reduced in newborns, we wished to determine the total coagulation defect. When the thrombotest percentage (TT%) falls below 10 per cent there may be danger of bleeding. We further wished t assess the prophylactic and therapeutic effect of vitamin K measured by the TT% in healthy newborns after normal delivery.

(1) In 1 newborns within 1 hour after birth the TT% in most cases ranged from 20 to 50 but a few infant presented values below 10 per cent ( ) The TT% was followed daily in 28 newborn infants who had not received vitamin K. In 16 infants the TT% fell below 10 per cent in 4 on the first day of lif in 7 on the second day of lif in 4 on the third day of lif and in 1 on the fifth day of lif. On the second day of life one of these infants developed symptoms of cerebral hemorrhage. Autopsy confirmed the diagnosis. There was no quantitative difference in the milk produced by the 16 infants mothers and the remaining infant mothers. (3) Twenty four newborns were given 1 mg menandion (vitamin K "Y eo") intramuscularly immediately after birth. During the first week of lif daily TT% determinations showed values ranging from 15 t 50 per cent and the mean curve showed a steady rise. In one infant the TT% fell below 10 per cent on the third and fourth days of life. (4) In 29 newborns who were given 1 mg menandion perorally soon after birth corresponding values were found. There were no low values. (5) In 30 newborns who received 3-5 mg phytonandion (Konakion "Roche") perorally directly after birth there were no low values in the course of the first week of life, and the mean curve rose more rapidly than under points (3) and (4). (6) The 16 infants whose TT% had fallen below 10 were all given 3-5 mg phytonandion perorally and after 20 hours the TT had risen well abov the bleeding threshold. (7) Fifteen mothers were given 20 mg phytonandion 4-24 hours before delivery. The dail TT of their babies showed no low values (all above 20 per cent). In one case the interval between medication and delivery was only 3 hours, and the infant TT fell below 10 per cent on the second day of lif. (8) Comparison between the mean curves of vitamin K treated patients may give the impression that phytonandion orally administered gives better results than menandion intramuscular or orally administered, but in values exceeding 50 per cent the TT method is unreliable. In consequence the curves do not allow definit conclusions. However since phytonandion takes effect more rapidly in overdosage with dicumarol and does not cause inclusion body formation and hyperbilirubinemia, it seems reasonable to use it in the prophylactic and therapeutic treatment of newborn infants.

Conclusions. The coagulability of the blood of newborn infant is reduced. In some infant the coagulation defect becomes so marked during delivery or in the course of the first few days of lif that there is real danger of hemorrhage. This danger may be prevented by vitamin K treatment. Administration of vitamin K to all newborn infant should therefore be instituted as a preventive measure either by treating the mother 4 t 4 hours before d livery or by giving the infant phytonandion immediately after birth. Oral administration gi es as good results as parenteral administration.

DISCUSSION

Leif Salomonsen. Even if the investigations reported by Doctor Wefring concern previously well known conditions it is important to have the earlier findings confirmed by a more reliable technique than the one on which our previous experience has been based. I was particularly struck by the st tement that the TT% was not affected by the amount of milk given to the infants. This rather conflict with the est blished view that marked degrees of hemorrhagic tendency usually occur in infants who get little mother milk. Hemorrhagic disease in the newborn was far more frequent 20-25 years ago than it is today and one must suppose that this is connected w th the fact that t that time feeding was delayed as a

matter of precaution, whereas today we start feeding the infants when they are about 12 hours old.

Arne Kdss Since the present investigations show that a real risk of hemorrhage is present in every newborn infant, there certainly seems to be indication for extending the prophylactic vitamin K treatment of newborns to embrace all newborn infants and not only those especially threatened. In Vestfold County Hospital 2 mg phytonandion (3 drops of Konakion) is administered orally to all infants as soon as possible after birth and, where it has been necessary after aspiration. Premature and fullterm infants whose condition prevents oral administration are given 1 mg phytonandion intramuscularly (0.5 ml Konakion) As the risk of hemorrhage may be present from the moment of birth the best thing seems to be to *give the mother vitamin K therapy at the* onset of labour Routine administration of phytonandion would be very expensive, but menandion treatment is much cheaper However such medication will not become standard treatment until after thorough examination of the serum bilirubin concentration in the neonatal period as affected by the mother having been given menandion and the infant possibly phytonandion.

Margrethe Wehn If larger-scale investigations confirm the findings reported prophylactic administration of vitamin K to all newborns (before or after delivery) would seem essential However the oral administration which has been recommended here tonight holds an important factor of uncertainty in that vomiting occurs so very frequently in newborns. In all cases where adequate administration of vitamin K has not been seen to before delivery I therefore believe intramuscular administration to be the most appropriate method.

C F Borchgrevink I believe it is important to keep in mind that the thrombotest was devised as a control measure in anticoagulant therapy As liver function test in the 50–100 per cent range the test is less suitable, as it is not very sensitive at such values. Doctor Wefring findings pertaining to low values seem to me convincing On the other hand, I hardly think one would be entitled to draw definite conclusions as to the best way of administering vitamin K from small differences in the TT% at the 60–80 per cent level. Both experimental and clinical studies reveal that if the TT% in adult patients receiving anticoagulant therapy falls below 10 per cent the bleeding tendency increases considerably On the other hand, there is no reason to overestimate the risk In our experience this low level has to persist for quite some time before spontaneous bleeding occurs. It can probably not be taken for granted that our experience with adults applies to newborn infants as well. But, all things considered, it seems reasonable to draw the conclusion from Doctor Wefring' findings that vitamin K should be administered to the mothers during *the twenty four hours prior to delivery* as a matter of routine

H M Svendsen. Mental prognosis in infants with hypothyroidism

A study of 26 patients with congenital hypothyreosis is presented. After a period of observation ranging from 4 to 8 years, the patients were re-examined with special regard to mental attainment. All the patients have exclusively been treated with l thyroxin Na. According to severity of the disease the material was divided into two groups which were considered separately: (1) severe congenital hypothyreosis in 14 patients with symptoms before the age of 6 months and (2) mild congenital hypothyreosis in 12 patients with gradually appearing symptoms between 6 to 18 months of age Thirteen patients in the first group received adequate treatment Four of these patients had normal intelligence, the remainder displayed more or less mental retardation In 3 patients with normal intelligence treatment was started very early In 5 mentally retarded patients, however therapy was also commenced at a fairly early point of time Eight patients in this group had a prolonged neonatal icterus. In the second group 9 out

of 1 patient attained normal int lligence Among the 3 retarded patients, 1 patient received inadequat treatment and in 2 patients therapy was very much delayed A normal EEG tracing was obtained in 8 patients with normal intelligence and in 6 patients with mental retardation, while a pathological EEG was found in 5 normal and 7 retarded patients. It is concluded that the mental prognosis in children with severe con genital hypothyreosis is dubious. Many patients remain mentally defective in spit of early and dequate treatment A prenatal thyroxin defect due to an insufficient transplacental passage of the thyroid hormone may be responsible for this disappointing fact. In children with mild congenital hypothyreosis the mental prognosis seems to be good In both forms of the disease the best result with regard to mental achievement is obtained by early and adequat therapy The frequent occurrence of a prolonged neonatal icterus in severe congenital hypothyreosis and the importance of this finding is stressed The prognostic value of EEG tracings is limited in the individual case Treatment with 1 thyroxin N is entirely satisfactory and seems more rational than the use of dried gland preparations.

DISCUSSION

Roald R rd. Doctor Svendsen findings are indeed discouraging, particularly as one was under the impression from previous investigations that if treatment was instituted at about 6 months of age the prognosis was fairly good. Marv el's rates from Norway and, even more statistics from Finland from the thirties all pointed in that direction. The accepted view was that the treatment had to be initiated with small doses of thyroxodine In Doctor Svendsen material thyroxine has been used in the substitutional therapy Can it be right t employ this pure bemical compound? A several hormones are present in the thyroid gland it might be a mistake to make use exclusively of the thyroxine In the Pediatric Department Ullevål Hospital, we employ the dried gland which seems of very good effect W ha e not arranged our material in the same excellent manner Doctor Svendsen has done but our impression, for what it is worth, is that the prognosis for our patients is better For that matter we are in good company in employing thyroid since it is used, for instance in Wilkins Clinic and probably in the other bigger American hospitals too In the last number of *Acta Paediatrica* Zetterström reports that in a material of patients with Hashimoto disease which is a form of hypothyroidism, he employed dried thyroid gland with very good results.

Heinrich C. Sommerschild The nephrotic yndrome —steroid treatment

Fifteen patient with the diagnosis of nephrotic syndrome, have been treated in the Pediatric Department Ullevål Hospital, during the decade 1950–60. The diagnosis seems unquestionable in all cases, and the possibili ty of "type II nephritis can practically be ruled out No patient had received steroid treatment before admission to the hospital. All were admitted after having been ill only a short t me t most a couple of weeks. The age distribution at the onset of the disease ranged from 3 months to 6 years, which gives an average of 2.7 ears.

Treatment. Treatment with ACTH in the dosage of 25–100 mg per day or predni sone (15–40 mg per day) was kept up for 10 to 20 days. Cortisone was given in two cases in the dosage of 40 mg and 100 mg per day respectively for 10 days. Maintenance treat ment consisted of either 30–40 mg predni sone per day the three first days of the week, or 5–10 mg daily for t least 6 months. In one case ACTH in the dosage of 30 mg twice a week, later once a week, was given. This treatment was kept up for 6 months. N other medicinal or dietary regimen has been regularl employed.

Observation period. The observation period ranged from 29 months to 103 months, average 58.5 months, from the time of ad mission. A erage duration of freedom from symptoms is 51 months for the patient who are symptom-free today

matter of precaution, whereas today we start feeding the infants when they are about 12 hours old.

Arne Kåss Since the present investigations show that a real risk of hemorrhage is present in every newborn infant, there certainly seems to be indication for extending the prophylactic vitamin K treatment of newborns to embrace all newborn infants and not only those especially threatened. In Vestfold County Hospital 3 mg phytonandion (3 drops of Konakion) is administered orally to all infants as soon as possible after birth and, where it has been necessary after aspiration. Premature and fullterm infants whose condition prevents oral administration are given 1 mg phytonandion intramuscularly (0.5 ml Konakion) As the risk of hemorrhage may be present from the moment of birth the best thing seems to be to give the mother vitamin K therapy at the onset of labour Routine administration of phytonandion would be very expensive, but menandion treatment is much cheaper However such medication will not become standard treatment until after thorough examination of the serum bilirubin concentration in the neonatal period as affected by the mother having been given menandion and the infant possibly phytonandion.

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revealed pathologic conditions in the form of a more or less marked dilatation of the ventricular system in all cases. PEG was also carried out on patients presenting the primarily complicated picture disclosing similar pathologic findings. One of these patients had sequelae the other only pathologic EEG changes.

Conclusions Following purulent meningitis sequelae have been demonstrated more frequently in patients presenting a primarily complicated course particularly where subdural effusions were present, than in patients with a primarily uncomplicated course. Special attention should be given to subdural effusions as this is a condition that can be treated.

S Halvorsen Oul

Swedish Pediatric Society

Meeting March 10 1961

K. H Gustavson Chromosomal abnormalities in two mongolism-like syndromes

Published in *Acta Pediat 50* 40, 1961 (J A Böök, K. H. Gustavson and B Santesson).

B Werner Aspects of adoption of children from the maternity wards

Eighty nine newborn infants whose mothers suggested adoption while at the maternity hospital (Södersjukhuset, Stockholm, 1959–60) were studied as regarded the motives for the adoption plans and as regarded the opportunities the biological mothers had to change their minds and assume care of their infants. The reasons most often given for the adoption offer was a bad economic situation and or bad housing facilities (5 cases). When the situation in the neonatal period was compared with the situation a few months later a marked difference was found, as half of the mothers had been able to take care of their infants themselves—35 had gone to the mothers and 31 to infant homes for later adoption (23 cases not settled at the time of report). Two factors are stressed as essential in making this change possible: (1) available beds for these babies in infant homes, where they can be admitted directly from the maternity wards, and (2) existence of social workers familiar with the problems in this field (all cases had passed the Adoption Board of the city of Stockholm). During the period of the baby stay at an infant home the mother gets the necessary time to be able to arrange for herself and her child. The experienced social worker can provide guidance in a neutral way helping the mother to work through her problems and make her see alternatives if they exist. A follow-up is planned as regards the future situation for the biological mother with and the mother without the baby

A Alm Intracranial aneurysm in children

The commonest kind of aneurysm in children is the arterio-venous type. The saccular type occurs also. With regard to the etiology of these the former are congenital defect and the latter are probably secondary to congenital defect in the media at arterial bifurcations.

Symptoms Headache is not especially common in children with aneurysm, provided that rupture has not occurred. *Focal neurological symptoms* of different types can be caused by large cortical arterio-venous aneurysm. One should be especially suspicious of simultaneous occurrence of high intra

cranial pressure, trauma or infection. Repeated *focal convulsions* without signs of high intracranial pressure high fever trauma in the past history or any other distinct abnormality should raise the suspicion that a vessel anomaly is present. The EEG may in such cases show signs of focal changes f unspecific a well as epileptogenic type Spontaneous *intracranial hemorrhage* (subarachnoid, intracerebral or a combination of these two) is the most serious complication of an intracranial vessel defect. Symptoms vary from only a headache of rapid onset with hyperactive reflexes without local neurological signs, to hemiplegia, aphasia convulsions and coma. If a unilateral *intra cra ial murmur* is heard, it indicates that a blood vessel anomaly is present. The absence of thi does not rule out aneurysm, however Four cases with intracranial aneurysm are presented in brief

Case 1 Male. Convulsions since the age of three days, which increased in frequency when the patient lay on the right side Encephalography showed right-sided atrophy An exploratory operation at four month of age revealed a very large right sided cortical arterio-venous aneurysm. Death —*Case 2* Male. Congenital heart disease At the age of 7 years, subarachnoid hemorrhage. Angiography by the vert bral artery showed an aneurysm of the posterior cerebral artery the size f a hazel nut Before heart surgery a new angiographic study was mad with the catheter in the left subclavian artery This revealed an arterio-venous fistula at the level of the tlas. *There was no filling of the aneurysm which* had previously been demonstrated. Operated upon for supravalvular aortic stenosis. No further intracranial hemorrhages have occurred Effect of the fistula at the atlas? —*Case 3* Male Subarachnoid hemorrhage at the age of 5 years. Encephalography showed widening of the septum pellucidum Cyst? At 9 years of age two new episodes of subarachnoid hemorrhage. Angiography and operation showed a large arterio-venous aneurysm in the third ventricle.—*Case 4* Female 13 years old. After an episode of physical and mental stress suddenly unable to read or write. General tremor Initial diagnosis: Hysteria? Operated upon the following day for a large intracranial hematoma which arose from a small aneurysm

The importance of microscopic blood vessel changes of the type seen at arterio-venous aneurysm which cause idiopathic, spontaneous intracranial hemorrhages in children is discussed

Addendum Just a week after reading this paper a fifth case arrived in the Sachs Children Hospital.—*Case 5* Female, 7½ years old Normal development. Quite healthy Acutely ill with frequent vomiting and sligt t fever (38,3°C) Somnolent. Babinsky sign positive on both sides. Slow light reaction of the pupils. EEG showed severe abnormality on the right side Angiography by using the carotis artery on the right sid revealed a large tumor very rich in vessels in the middle parietal region. At operation it was found to be a large arterio-venous aneurysm with a hematoma Control angiography by right and left carotis artery showed that one-quarter of the aneurysm was left Now in good condition. Re-operation after half a year

Per J N rde felt Th child' foot: some pediatric points f view

(1) The child foot has a narrow heel and a wide forepart, widest over the tips of the toes. (2) A large percentage of children have from birth, a physiologic foot weakness (pes planovalgus) which disappears at 5–8 years of age They also have a physiological genu valgum from 1½ to 7–8 years of age. (3) Children in the pre-school age practically never stand still on their feet if they do not have to do so Children of school age *stand* for only very short periods. (4) The cond tion of the foot and its functional capacity depends to a great extent on muscle tone and strength (5) The prevention of foot weakness in childhood is based on the principle that the musculature of the whole body should grow and develop t its f llest capacity Going barefoot as much as possible both

indoors and out of doors; for some children cautious training in walking on hard paths and streets; eventually foot exercises; suitable shoes and stockings. (6) Firm boots and shoes as well as arch supports are effective only when the child is in a standing position.

Hilding Wetterstein. Is congenital pes calcaneo-valgus the cause of flat feet in children?

The author has previously reported (*Acta Orthop Scand 30*; 64, 1960) on a study concerning the significance of congenital calcaneo-valgus which is often present in newborns. Some consider that in certain circumstances this condition may lead to pes plano-valgus when child begins to put weight on his feet. Such an association has not been shown by any systematic study.

During a two-year period, all newborns (2,725) in the obstetrical unit of Jönköping Hospital were examined. Evidence of congenital pes calcaneo-valgus of a considerable degree was seen in 5.2% (Group 1) of moderate degree in 12.1% (Group 2) and of lesser degree in 27.7% (Group 3). There was no evidence of this condition in 54.6% (Group 4). One hundred children in each group were examined after an interval of one year. At one year of age the frequency of pes plano-valgus in Group 1 appeared to be greater than in children of the other groups. The difference was greatest on comparison with an unselected group of infants from Group 4. The investigation when continued until two and three years of age indicates that a levelling off of the incidence occurs, in that the number of cases of pes planovalgus in Group 3 and 4 increases. No significant difference in the incidence of pes plano-valgus appears to be present between children with congenital pes calcaneo-valgus during the newborn period and children without this condition. Further investigations of older children should be made before a definite conclusion can be arrived at.

Meeting April 7 1961

Carl-Axel Ekman and Åke Grewik. Intestinal rotation anomalies

The authors presented a series consisting of 40 patients (36 children and 24 adults) with anomalies in the embryological rotation and fixation of the alimentary tract, seen during the period 1951 to 1960. The cases have been classified in accordance with Estrada criteria. Seven children had omphalocele all with non-rotation of the bowel. Twenty two patients had mixed rotation, and of these 17 also had small bowel volvulus with obstructive symptoms as early as the first few days of life. Surgery was required for intestinal obstruction in 14 of these. Non-rotation occurred in 14 patients. In 1 such cases the anomaly was an incidental discovery during treatment of other conditions. Seven patients had anomalies of more unusual type. In 10 patient with fixation anomalies the condition was first recognized during adult life. Only 4 of these patients had symptoms attributable to their anomalies. Roentgen examinations have been of great importance in diagnosis. The series shows, however that both the duodenum and the caecum may be normally situated in the presence of errors of rotation and fixation. The operative method used have been those current generally such a Ladd operation for mixed rotation and Gross s operation for omphalocele. There were eight deaths in the series, all in neonates. Other complicating anomalies were present in 35% of the patients and these were responsible for six of the eight deaths. In only tw children was death attributable to malrotation.

O Orist. Surgical treatment of hernia i to the umbilical cord

Omphalocele or hernia into the umbilical cord, is congenital malformation. The hernial sac, consisting of peritoneum and am

mion may vary in size. It may contain only small intestine or it might include most of the large and small intestine as well as part of the liver and stomach. Omphalocele is a rare condition and occurs about once in every 10 000 births (Jedberg, *Acta Obstet Gynec Scand*, 1942). Associated anomalies occur with more than coincidental frequency. Gross (Boston) found such anomalies in 59 % of his series and occasionally these were serious. The treatment of an omphalocele is surgery and it should be performed immediately. It is simple in small hernias and the prognosis is good. A large omphalocele, on the other hand, is a severe condition with high mortality even in good hands. At Kronprinsessan Lovisa's Children Hospital, 23 patients were operated upon from 1942 through 1960 (11 boys and 12 girls). Birth weight varied between 1720 and 5000 g. Associated anomalies occurred in 13 cases. Of the 22 children, 9 had a small hernia and 14 a large one. Radical operation in one stage was performed in 16 cases, and a two-stage reconstruction of the omphalocele was planned or carried out in 7. There were 12 survivors and 11 deaths, the majority of these due to respiratory distress. The last two cases in the series are described. Both had a large omphalocele whose sac ruptured at birth. A two-stage reconstruction was performed and the defect of the abdominal wall was repaired by dissection and closure of the anterior rectus fascia. Both patients survived, made an uneventful recovery and have a satisfactory abdominal wall.

Gösta Ehrenborg and Bengt Engfeldt: The insertion of the ligamentum patellae on the tibial tuberosity: some views in connection with the Osgood–Schlatter lesion

For almost 60 years the etiology of the Osgood–Schlatter lesion has been debated, but the problem cannot be regarded as fully solved. Recent clinical and histologic studies (Ehrenborg et al. 1961) suggest that its etiology is traumatic. The present report concerns an investigation of the anatomic and mechanical prerequisites associated with a traumatic origin of the Osgood–Schlatter lesion in the age groups relevant to the lesion. Most of the power of the *quadriceps femoris* was found to be projected onto a narrow zone at the craniolateral limits of the tibial tuberosity. Ossification of the tuberosity begins in the caudal portion of Hence's disc. In this apophyseal stage, when the symptoms of Osgood–Schlatter lesion usually appear, most of the ligamentum patellae is inserted into cartilage within the zone which receives most of the force of the quadriceps. Therefore, if the force which is delivered exceeds the tensile strength of the attachment, larger or smaller fragments of cartilage will be torn off and dislocated. The results of this study support the concept that the etiology of the Osgood–Schlatter lesion is traumatic. The causal mechanism would seem to be avulsion of the cartilaginous attachment of the ligamentum patellae with consequent detachment of fragments of cartilage from a limited area on the cranial and lateral part of the tibial tuberosity.

S. Söderlund and B. Zetterström: Cholelithiasis and cholecystitis in children

From 1950 to January 1961 59 children between the ages of 6 to 15 years of age were operated upon for cholecystitis and/or cholelithiasis at Kronprinsessan Lovisas Barnsjukhus. Etiological factors of significance were hemolytic anemia (3 cases) and diverticulum of the gall bladder (2 cases). Heredity did not seem to be of any definite importance. Body weight in most cases was at the upper limits of normal. The sex incidence was 56 females and 3 males. Acute cholecystitis occurred in 5 cases. Chronic cholecystitis was present in 31 cases, of which 28 had stones. Twenty-two patients had cholelithiasis without signs of inflammation, and only one patient had cholesterol stones in the gall bladder. One patient had acute pancreatitis. All patients had abdominal pain, and 46 of them localized the pain, on at least one occasion, in the epigastrium or the right upper quadrant. The younger patients indicated that the pain

was diffuse or was found near the umbilicus. Pain related to meals was noted by 1 patients. Vomiting and nausea were often mentioned. Abdominal palpation was nega ti e in 23 patients on at least one occasion. Tenderness in the right upper quadrant was often present and was over the MB in 10 cases. Ten patients had an elevated sedi mentation rat and 6 were icteric, of which 3 had hemolytic anemia. Cholecystography showed stones in 41 cases, while in 8, the gall bladder did not fill with contrast. In 30 cases, the symptoms were so typical that disease of the gall bladder was suspected t once. In the remaining cases, the diagnosis was not clear for a long time. Unspecific, dif f se, recurrent bdominal pains were reasons why several patients were repeatedly hospitalized with a diagnosis of umbilical colic mesenteric adenitis, constipation or psychogenic pain. Appendectomy wa performed in 11 cases beca se of suspected acute or chronic ppendicitis. Eight patient had symptoms for 6–10 years before correct diagnosis was made. Cholecystectomy was done in 58 cases; in 2 cases of hemolytic anemia a splenectomy was carried out at the same time. In the third case of hemolytic anemia, holecystotomy was done in addition t a splenectomy. N postoperative complications occurred. One patient was reoperated pon because of intestinal obstruction caused by adhesions 2 months later and has been well since. Following cholecystectomy 3 patient have had pains simulating an acute gall bladder attack.

Lub g Ohman nd Göran Südow. Acute duodenal ulcer associated with burn injuries in children

A large percentage of the cases of duodenal ulcer associated with burns (Curling ulcer), occur in children. Thi has been explained by the large number of burn injuries in childhood. In the surgical department of the Pediatric Clinic Karolinska Jukhuset during the years 1952–1960 328 children with burns have been treated. Eight died and came to autopsy. 2 had duodenal ulcers. One of these a 14-month-old boy with proportionally small second-degree burns (20%) went into shock 12 hours after the injury and presented pronounced hemoconcentration. Melena was noted 40 hours after injury and death followed after 7 days of gastrointestinal bleeding. The other case, that of a 3-year-old boy with 80% third degree burns, required extraordinarily large quantities of colloids to prevent shock. H presented vomiting on the first day and developed melena by the ninth day. Vomiting increased and resulted in nutritional disturbances and death after 26 days. The course in both these cases supports Friesen xperimental findings that hemoconcentration is an essential predisposing factor in the tiology of duodenal ulcers secondary to burns. The ratio between body surface and body weight is greater for children than for adults. A similar relationship exists for body surface area and plasma volume which make p about 5% of the body weight. The amount of plasma of a child per surface area skin is thus less (a child with a body weight of 10 kg has a value of only 40% of that of an adult). The risk of hemoconcentration and Curling ulcer (according to Friesen) is therefore theoretically greater in children. The supplying of colloid (shock therapy) influences the plasma volume and hemoconcentration. By using a dosage formula based on the amount of colloid per kg body weight (for example Evan formula) child weighing 10 kg will receive only half as much colloids per surface area burn injury as the adult of 70 kg weight.

Summary. Constitutional conditions make the risk of duodenal ulcer following burns greater for children than for adults. Adequate shock therapy calculated according to body surface area and continuous hematocrit determinations probably decrease the risk of this complication.

Meeting April 24 1961

Dr Deborah Doniach (the Middlesex Hospi tal Medical School, London) Auto-immune thyroiditis

Meeting May 27 1961

B Vahlquist International Paediatric Association. Points of view

A short review is given of the present-day activities of the International Paediatric Association. Increasing demands necessitat certain changes in the organization of the Association, and 10 paediatricians therefore met in Zürich in April 1961 The main points of the report of this meeting were pre sented for discussion.

M M'chaelsson Studies on methods for th determination f serum bilirubin

The standardization of methods for the determination of serum bilirubin is discussed. A new chemical reaction is described in which a complex between bivalent copper and diazotized bilirubin is formed The two diazo-coupling methods of Malloy–Evelyn and of Jendrassik–Grof (as modified by Nosslin) are compared. The material con sists of sera obtained at exchange transfu sions The Jendrassik–Grof Nosslin method is preferred to that of Malloy–Evelyn A modification of the Jendrassik–Grof–Nosslin method is described, by which errors due t haemolysis and turbidity in the sample are avoided, and probably more reliable figures are btained for direct reacting bilirubin.

V O Björk, Herm n Lodin and P O Petersson. The surgical treatment of abnor mal venous return with o without atrial septal defect

At the present time a variety of methods are available for the correction of abnormally returning pulmonary veins. Sixteen cases (6 children and 10 adults) were studied with heart catheterization and selective an giocardiography before and after operation. There were 2 cases with totally abnormal venous return one operated on under deep hypothermia and the other at normal tem perature using the heart–lung machine in both cases with very good results. Fourteen cases with abnormal venous return from the right lung into the superior vena cava, right atrium or inferior vena cava were perated upon openly under hypothermia witl coronary perfusion using one of the following methods

(1) The abnormally draining vein was left untouched if it entered the superior vena cava high up It is advisable to prevent too long and narrow a channel with obstruction of the superior vena cava after partitioning (2 cases) (2) Internal part tioning of the superior vena cava and pulmonary vein into two channels according to Lewis (2 cases) (3) External partitioning of the common stem of the superior vena cava and of the right pulmonary veins before the right atrium is opened. The atrial septal defect is then closed so that the abnormal veins drain into the left atrium through the defect (7 cases) (4) Division and re-suture of the pulmonary veins into the left atrium was used in 2 cases with an intact atrial septum. In one case with the total venous return from the right lung into the inferior vena cava, the left atrium was too small to permit direct suture, so that after partitioning the veins were sutured into the right trium and were then connected to the left atrium through the atrial septal defect (5) Abnormal venous return into right trium i the easiest con dition to deal with. The atrial septum is placed over the veins at the same time as the defect is closed (1 case)

The patients were investigated on the average nine months after operation, in particular to test the patency of the pulmonary venous opening into the left atrium.

There was no mortality during or after operation, and there were not even any severe postoperative complications. At re-catheterization no residual shunt could be detected, even in cases where an abnormal vein from the right lung entered the superior vena cava high up and had been left untouched at operation. There was no pressure gradient between the superior vena cava and the right atrium as a result of postoperative obstruction. At selective angiocardiography no obstruction of the venae cavae or the operated pulmonary veins could be detected. Moderate increased pressure in the right ventricle and signs of hypertrophy in the ECG returned to normal. The size of the heart at roentgen examination was reduced in all cases.

It seems to be very important for the surgeon to be able to vary the surgical technique according to different anatomical variations. Abnormal venous return from the right lung combined with atrial septal defect of sinus-venosus type was most common and in these cases the so-called external partitioning seems to be the technique of choice. There seems to be no indication for using the extra-corporeal circulation in these cases.

Anne-Marie Hedenius, Bengt Hagberg, Karin Hyttnäs Bensch and Irene Sjögren. The natural prognosis of infantile hydrocephalus

The natural history of infantile hydrocephalus was investigated in 180 untreated patients (113 boys, 67 girls) who had been admitted under this diagnosis to the Paediatric Clinics at Uppsala, Boden, Linköping, or Örebro during the years 1944–1958. Only cases in which an abnormally rapid increase of the head circumference had taken place during the first year of life were included.

Ninety-five patients were found since to have died (45 boys and 50 girls). Death was due to meningomyelocele in 35, cerebral tumour in 2, and unarrested growth of the skull in 58 cases. In the last group many children had died in a state of hyperpyrexia without any other signs of infection; cerebral fever was therefore probably the cause of death. Of 97 children in whom the abnormal growth of the skull had stopped, 77 were still alive and 20 had died.

Altogether 85 children, 68 boys and 17 girls, were found to be alive at a preliminary follow-up investigation, which in many cases only consisted of collecting information from parents, teachers, district nurses, and other doctors. The series was grouped as follows.

Mental development

"Normal"	42 (33 boys and 9 girls)
"Educable	20 (15 boys and 5 girls)
"Ineducable	23 (20 boys and 3 girls)

Motor function

"Normal"	40 (33 boys and 7 girls)
"Slightly handicapped	29 (21 boys and 8 girls)
"Severely invalidized"	16 (12 boys and 4 girls)

The social adjustment was enquired after in all patients over 8 years of age: 31 children in all. Half of these (10 boys and 6 girls) were said to be well adjusted in school and society and accepted as ordinary children. Fifteen were characterized as odd with mental or motor defects or both. Ten boys and one girl were severely retarded institutional cases.

Thus half of the survivors with spontaneously arrested skull growth were found to be doing surprisingly well, even if some of the apparently normal children may prove to have minor mental and physical handicap on more thorough examination. No direct correlation was found between the degree of cortical thinning found on encephalography and the intellectual capacity which tallies with the fact that patients with a cortical thickness of 1 cm or less are known still to be within normal intellectual limits.

Of the survivors 22 have so far been reexamined. Nine of them were found to have dysplastic body build with abnormal distribution of the fat to the hips, buttocks and lower parts of the abdomen. In 14 cases valgus deformity of the feet was a prominent finding. Special interest was directed to neurological and mental symptoms and signs characterizing the hydrocephalic state. Some

degree of ataxia was found in no fewer than 16 of these patients. In addition, hypotonia and hyperflexibility especially of the lower limbs, seemed to be a very characteristic sign, and was most commonly seen during the early years of life: it was found in 10 of the 23 patients on examination but to judge from the histories had probably been obvious during earlier years in some others. Other signs of cerebral palsy mainly diplegia, were found in 8 of the atactic and 2 of the non atactic children. Severely impaired vision with optic atrophy was found in 5 cases, squint was present in 15, 11 of them showing the divergent type. Only three children were neurologically completely normal. Hydrocephalic children were often found to be mentally retarded but educable, with a peculiar contrast between a good ability to learn words and talk, and not knowing what they are talking about. They love to chatter but think illogically a feature which we have called the cocktail party syndrome. This syndrome was found in 6 of our 23 cases.

The following points were made regarding hydrocephalus, its prognosis, and its operative treatment by the ventriculo-venous shunt operation: (1) Congenital hydrocephalus is not a clear-cut disease-entity but a syndrome that may be secondary to any one of a great diversity of underlying lesions. (2) The long term prognosis, and in particular the degree of mental and physical handicap, seem to depend more upon the nature of the underlying cerebral lesion than upon the degree of hydrocephalus. (3) The flattening out of the brain tissue that takes place in progressive hydrocephalus seems to cause moderate, relatively slowly developing derangement of motor and mental function. Even when the cortex is reduced to 0.5–1.0 cm in thickness the intellect and motor function may be practically intact. (4) In a surprisingly large proportion of cases of hydrocephalus the process shows a tendency to become spontaneously arrested after some time. (5) In the light of these facts and until further experiences are gained it would therefore seem reasonable to delay the ventriculo-venous shunt operation in cases of communicating hydrocephalus appearing late and progressing slowly. Operation should be considered without delay however in all early rapidly progressive cases.

G. Grotte: Surgical treatment of hydrocephalus using the Spitz Holter ventriculo-atrial shunt.

Published in *Acta Pediat* 50: 617, 1961 (G. Grotte & N. G. Sundberg)

Meeting June 20, 1961

C. H. Kempe (Dept. of Pediatrics, Colorado University School of Medicine, Denver, U.S.A.): Recent advances in the study of smallpox and serious complications of smallpox vaccinations.

R. Lagercrantz, Stockholm

ANNOUNCEMENTS

X. International Congress of Pediatrics

This congress will be held in the University City buildings in Lisbon Sept. 9 to 15 1962. President is Prof Dr C. Salazar de Sousa and General Secretary Prof. Dr Mário Cordeiro. Address: Hospital Santa Maria, Av 28 de Maio, Lisbon 4 Portugal. Applications should be made not later than May 31 1962; those who are registered before Jan. 31 1962 pay 36 U.S dollars or 155 Swiss Frcs others have to pay 45 dollars or 195 Swiss Frcs.

The preliminary program for the Plenary Sessions is as follows:

First Plenary Session. *Problems of the Newborn*. 1 The development of the cerebral function. Prof. M. Lelong, France — The development of the renal function. Prof H. Barnett, U.S.A. 3 The development of the hepatic function. Prof G. Lathe England. 4 The metabolism of drugs during the new born period Prof. N. Kretchmer U.S.A. 5. Immunobiology of the new born. Prof. I. Nasso P Menghi and E. Grasso, Italy 6. Pulmonary diseases of the new born, Prof. P Karlberg, Sweden. 7 The prevention of brain disturbances in the newborn. Prof. O Thalhammer Austria. Prof. L. K. Diamond U.S A. and Prof G Joppich, Germany

Second Plenary Session. *Pediatric Problems of Tropical Climates and of Countries Development* 1 Child nutrition in early years. Prof A. Moncrieff England. 2. Sources of proteins in infant feeding. Prof. L. Garibay Mexico. 3. Amino acids and kwashiorkor Prof G Frontali, Italy 4. Prophylaxis and treatment of diarrhea in tropical countries. Prof. S. Achar India. 5. Rehydration. Prof J Senecal, Senegal. 6 The fight against tuberculosis. Prof. M Olinto Brazil. 7 The influence of parasitic diseases on the growth. Prof J M. da Rocha, Brazil. 8. The problem of anemias. Prof. E. Stransky Philippines. 9 The education of mothers. Madame Chavenon, Madagascar 10 The adaptation of the infant to malnutrition. Prof J Meneghello Chile

Third Plenary Session. *Pediatric Doctrine* 1 Modern aspects and scope of pediatrics. Prof. M. Suarez, Spain. The contribution of pediatrics in the progress of medical science Prof E. Rossi, Switzerland. 3 University teaching of pediatrics. Prof. J Richmond U.S.A. 4. *The college of pediatrics. Prof. K.* Kubat Czechoslovakia. 5. The organization of postgraduat teaching of pediatrics. Prof A. Ross, Canada. 6. Recent bio research in pediatrics. Prof. H. Hungerland, Germany 7 Social pediatrics. Dr N. Masse France 8. The practice of pediatrics. Prof F Gomez, Mexico. 9 The role of the pediatrician as an advisor in problems of education. Prof. P Plum, Denmark. 10 The rights of the child in modern societies. Prof G de Toni, Italy 11 The teaching of preventive pediatrics. Prof B Vahlquist Sweden.

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Meeting June 20 1961

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_rnough several ___ Kretchmer U.S.A. ___rborn. Prof I, more or less interrelate_ ___ Italy 6 the adaptive process the key to these is the onset of breathing and aeration of the lungs.

The purpose of the present investigation was to study the pulmonary ventilation and the mechanics of breathing in the first minutes with special reference to the first breath in normal newborn infants.

ces of proteins in infant feeding. Prof L. Gariba_ Mexico. 3. Amino acids and kwashiorkor Prof. G Frontali, Italy 4. Prophylaxis and treatment f diarrhea in tropical countries. Prof S Achar India. 5. Rehydration. Prof. J Senecal, Senegal 6. The fight against tuberculosis. Prof M. Olinto Brazil. The influence of parasitic diseases on the growth. Prof. J M. da Rocha, Brazil. 8. The problem f anemias. Prof. E. Stransky Philippines. 9 The education of mothers. Madame Chavenon, Madagascar 10 The adapt tion of the infant to malnutrition. Prof. J Meneghello, Chile.

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Methods and Procedure

Respiratory volume changes and the intra-esophageal pressure changes were simultaneously recorded. The former were recorded with face mask by means of a reverse plethysmograph, the pressure changes through water filled polyethylene catheter connected to an electromanometer

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One of series of studies supported by research grants from the Swedish Medical Research Council and from the Association for the Aid of Crippled Children, New York City.

Boston Lying-in Hospital, 221 Longwood Ave Boston 15, Mass U.S.A.

Santa Fé 1050, Buenos Aires, Argentina.

Universitäts-Kinderklinik, Tubingen, Germany

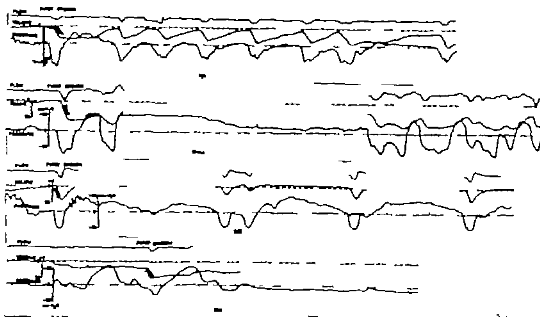


Fig 1 Recordings in four infants, Nos. 40, 43, 66 and 71 In each record the top tracing is the flow rat the next the volume and the third the intra-esophageal pressure.

The apparatus and technique have been described in detail in Paper I of this series [18].

Immediately after delivery with the infant placed adjacent to the mother's peri neum on the delivery table and the cord unclamped, the esophageal catheter was in troduced, the mask placed tightly on the face and the recording started. The shortest time to get the recording started was six seconds from the moment when the head appeared outside the vulva. Thus, the timing also in cluded the time for the complete delivery

In general, each infant was studied for three periods of ½–1 minute; the first as soon as possible after birth, the second at –4 minutes of age, the third t ½–1 hour of age. Some studies were repeated during the first week of life The result of these longitudinal studies will be published in a subsequent paper

Because of the effects of pressure in the water-filled system for measuring the intra esophageal pressure no absolut zero could be recorded. In each case the end-expiratory pressure during quiet breathing has been taken as the base line and pressure changes from this line are given. Since the pressure before the first breath was always constant and, furthermore, corresponded well with the end-expiratory pressures recorded later during the first recording period this pressure has been used as the base line for the first breaths.

Results

Volume changes

In 11 of the 18 infants the first clinically visible breath was recorded. In the remaining cases the recording started with the second to fourth visible breath The volume changes during the first recording period showed a wide variation. The recordings in four infants, each representing different patterns of onset of breathing are shown in Fig 1 The first infant (No. 40) had a rhythmic respiratory pattern *from the onset. The next two* (Nos. 43 and 66) had less regular breathing with tendency to periodicity The fourth (No.

TABLE 1 *Parity and age of mother, gestational age, birth weight, and recorded values*

Case no.	Parity	Age of mother	Gest. age	Birth weight kg	Res. start sec	Res. lgth sec	Record before 1st breath: Volume change Insp (+) ml	Record before 1st breath: Volume change Exp (−) ml	Record before 1st breath: Pressure changes + or −	1st recorded breath: 1st breath Time sec	1st recorded breath: 1st breath V_T/ml	1st recorded breath: If not 1st breath No.	1st recorded breath: If not 1st breath Time sec	V/V_T	V_R from 1st breath	V/20° from 1st rec. breath
39	II	29	39	3.30	30					30	33				0	630
40	II	30	40	2.61	24	8			+	33	38				5	453
41	II	28	41	4.33	44	11	−4	−4	2 + waves	55	60				30	352
42	I	25	41	4.18	14					—	—	IV/V	40	58	—	790
43	V	38	42	4.56	24	16		−23		40	67				17	204
46	I	21	40	4.00	75					—	—	IV	76	34	—	352
47	IV	30	40	4.37	23	1				23	60				30	296
48	II	29	39	3.43	18	6			+	24	12				−7	78
49	II	30	40	3.84	23					—	—	III	28		—	
64	I	23	42	3.68	10	7		−24	+ − +	17	17				8	300
65	I	27	37	4.40	6	1		−32	+ wave	7	24				4	650
66	II	31	37	3.63	3	3		−17	+ −	6	43				−9	241
71	II	27	42	3.73	80	13	+10		2 + waves	83	31				0	
74	II	31	41	3.58	11					—	—	II	16	53	—	300
75	II	27	41	3.05	29					—	—	IV	56	13.5	—	
76	II	25	38	3.55	15					—	—	III	15	30	—	500
78	III	31	37	2.36	13					—	—	II	14	8	—	
79	III	37	42	3.41	14	6	+36		Slight	30	62				5	

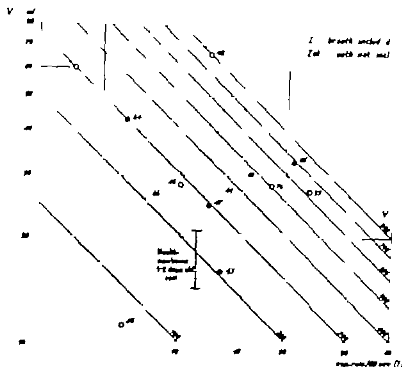


Fig. 2. Pulmonary ventilation during the first 20 second beginning with the first breath.

71) had a delayed onset of respiration he was the only infant who was considered to be slightly depressed

The magnitude and the time of the first recorded breath for each baby is given in Table 1 The respiratory tidal volume of the very first breath ranged from 12 to 67 ml. In 9 of 11 it was within the range of 31–67 ml.

In all infants the first breath was char acterized by a distinct short inspiration followed by a more prolonged and varying expiration, which in most cases proceeded slowly and irregularly No end-inspiratory pause was observed Often a second short inspiratory phase of considerably less magnitude than the first appeared and was followed by another prolonged ex piratory phase Thus in most infants the first breaths were characterized by long lasting expiratory phases with relatively short inspiratory components (see Case 43 Fig 1) However some babies had short distinct expiratory phases with a definite end-expiratory pause (Case 66 Fig 1).

In each case the subsequent breaths in the first recording period showed a volume pattern similar to that of the first breath. The frequency varied considerably In order to obtain some idea of the magnitude of the first breaths the inspiratory tidal volumes during the first 20 seconds beginning with the first recorded breath were calculated in the fourteen infants with sufficiently long recording time (Fig 2) The 20 second mean tidal volume (V_T) and respiratory frequency (f) are plotted. Because a double logarithmic scale is used the 20

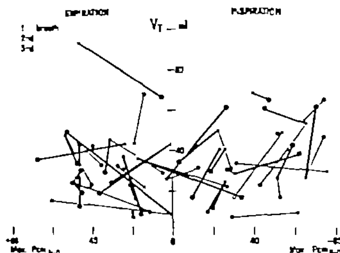


Fig. 2. Tidal volume range and corresponding intra-esophageal pressure changes during the first breaths. The straight lines connect values for each infant. Note that in several infants the inspiratory and expiratory tidal volumes are different (see text). The maximum positive pressure for each breath represents the differences between the pressure at the start of the inspiration and the peak pressure during expiration.

seconds volume ($= V_T \times f$) in each case can be evaluated from oblique lines in the chart. The mean tidal volume varied less than the frequency The effect of the first breath upon the inflation of the unaerated lungs should be seen in the difference between the inspiratory and expiratory volumes, i e a created *residual volume*. A volume difference of any considerable magnitude was found only in the cases where the first clinically visible breath was recorded but not even in all of these The residual volume in seven infants ranged from 4 to 30 ml In the remaining four cases either no volume change was recorded or the end-expiratory volume exceeded the inspiratory one by an amount up to 9 ml (Table 1) The net volume gain persisted during the following breaths a volume change compatible with a developing residual volume was never recorded in these infants

Intra-esophageal pressure changes

No appreciable negative pressure was recorded before the first clinically visible breath, although in a few infants there were some positive pressure waves (see below). In general the pressure was constant. During the first breath marked pressure changes were recorded, a sharp negative pressure wave during the inspiratory phase and a positive more prolonged and irregular one during the expiratory phase Similar pressure patterns occurred during the following breaths

The variation in both negative and positive pressures was considerable and pressures up to 70 cm H_2O were recorded. There was a general correlation between pressure and volume changes which was most apparent during inspiration Considerable disparity between individual patients is evident in Fig 3 The total pressure change during single breaths ranged

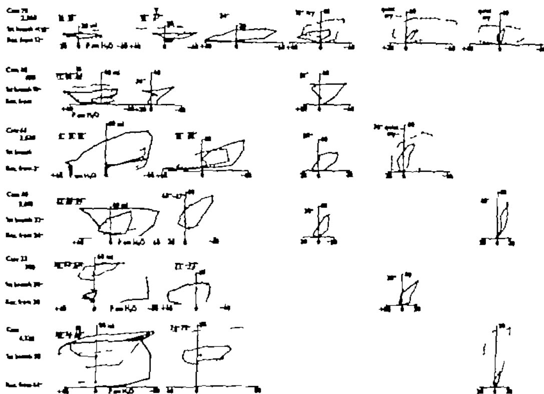


Fig. 4. Respiratory loops from six infants, Nos. 78, 48, 66, 40, 33 and 41. In the left half of each row are loops from the first recording period in the right half, representative loops from the following periods. In the first conglomerate of loops for each infant the loop of the first breath is drawn with heavy line, the one of the second breath with a broken line and the one of the third breath with a thin line.

from 40 to 100 cm H_2O. There were no striking systematic differences between the first second and third breaths. The pressure patterns during subsequent breaths of the first recording period were similar but in general were of decreasing magnitude.

The recording period *before* the first clinically visible breath ranged from 0 to 16 seconds. In this period no appreciable negative intra-esophageal pressures were recorded. However volume changes were observed. In some infants an inspiratory volume of 5–10 ml frequently followed by an expiratory phase was noted. Positive intra-esophageal pressures were recorded coincident with the increased volume. A slow inspiratory volume change constituting a residual volume amounting to 10–15 ml was seen in one infant (Case 71 Fig. 1). In some of the babies the onset of the first breath was preceded by an expiratory volume change of variable magnitude (10–25 ml) and simultaneously a positive pressure wave was seen.

Analysis of mechanics of breathing

The relationship between volume and intra-esophageal pressure changes through a whole breath is often used for analysis

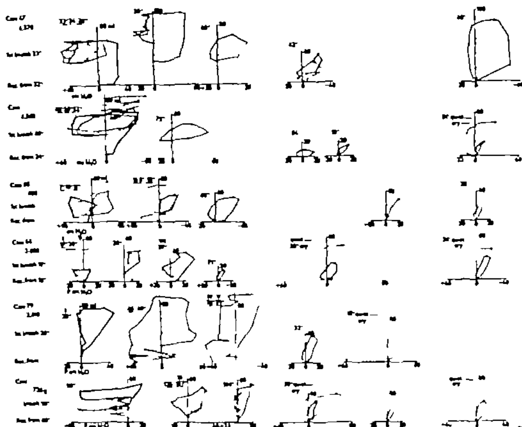


Fig. 5. Respiratory loops from six other infants, Nos. 47 43, 63 64, 79 and 71

of the mechanics of breathing since the intra-esophageal pressure change can be taken as representative of the sum of forces acting on the lung in producing the respiratory volume change [8]

In order to get further information about the mechanics of the first breaths, pressure–volume diagrams so-called respiratory loops have been constructed from the volume and pressure tracings [18]. The loops obtained from the infants in whom the first breath was recorded are shown in Figs. 4 and 5 (No 78 is also included).

The inspiratory part of the respiratory loop of the first breath has two different patterns. In infants Nos. 48 66 40 23 and 41 (Fig 4) there is a high initial increase in the negative intra-esophageal pressure before any marked volume change is recorded. The inspiratory loop has a square shape In infants Nos. 43 65 64, 79 and 71 (Fig 5) a very modest increase in negativ pressure immediately induces a volume change and the volume changes follow the pressure changes fairly rectilinearly to end inspiration The inspiratory part of this loop has a triangular shape

The expiratory part of the respiratory loop for the first breath i characterized

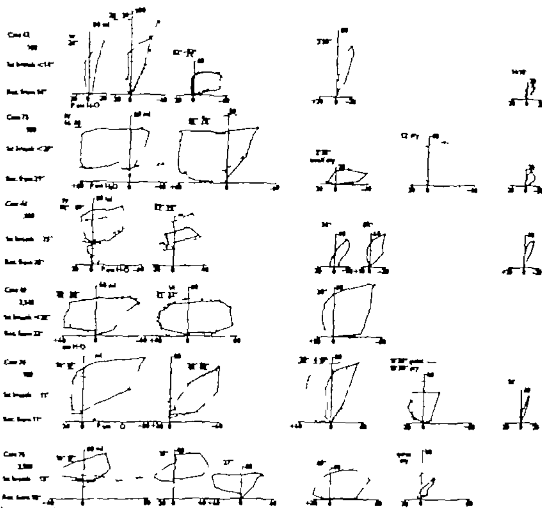


Fig 6 Respiratory loops from six infants, in whom the second to fourth breath was the first recorded one (Nos. 42, 75, 46, 49, 74 and 76).

in general by a very rapid pressure change from a high negative pressure to a high positive pressure before the volume starts to decrease

In the first group the respiratory loops of the second and third breaths become less square In the babies belonging to the second group (Fig 5) the end-expiratory pressure of the first breath is moved more or less towards the positive side (to the left in the loops) to + 20–30 cm of water This is also seen in No 41 (Fig 4) (In Nos. 71 and 79 the recording was discontinued before the second breath)

The respiratory loops in the infants in whom the first breath was not recorded are exemplified by the premature baby (No 8 Fig 4) The loops are about the same shape as for the fullterm infants if one considers the smaller tidal volumes Even in this infant the total pressure change i about 60 cm of H_2O Although the first

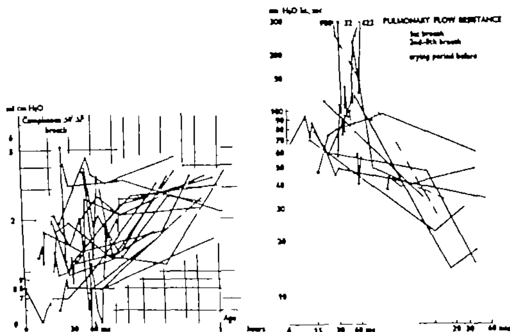


Fig. 7 and b. The compliance values ( ) and the pulmonary flow resistance values (b) are plotted against time on double logarithmic scale with the values of each infant connected by line t allow evaluation of any trend of changes in relation t ge. There is a clear trend for lung compliance to increase rapidly and for the pulmonary flow resistance to decrease fter the first few breaths.

and second breaths were not recorded in infant No 49 (Fig 6) the following four breaths show square loops. This lusty full term infant had very forceful retraction of the chest during each inspiration. The only other unusual clinical feature was that the umbilical cord ruptured just t the end of the delivery None of the other infant in this group had a square shape of the in spiratory part of the loops; otherwise they are similar to the infants in whom the first breath was recorded

With *increasing age* the loops become smaller and have decreased width during quiet breathing in all cases In some n- fants recordings were made during cry during the second or third recording period. These cry loops are ho for comparison in the right part of Figs. 4–6 These loops are large broad, and in general rounded and not square

The mechanical properties of the lungs in older children and adults are usually described in terms f *lung compliance* and *p lmonary flow resistance* [18] Because the loops obtained at half an hour of age and sometimes sooner indicate mechanical condition so similar to those later in life it seems reasonable to calculate the mechanical properties in neonates of this age group The resistive forces due to flow through the pulmonary tract cannot be separated from other non-elastic resistive forces by the method used. This i re grettable because one cannot separat th cohesive forces which are believed to play

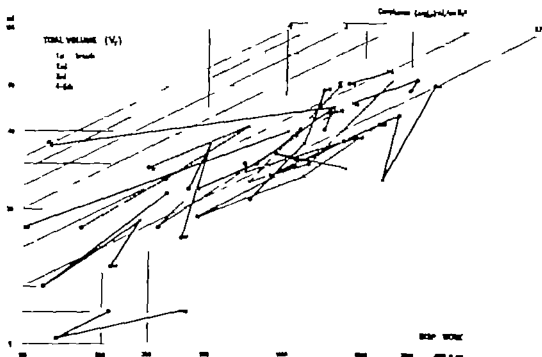


Fig. 8. The tidal volumes of the first three recorded breaths in each infant are plotted in relation to calculated inspiratory work. Since the volume change to the power of is approximately related to the required work (according to the Otis–Rahn–Fenn equation) double logarithmic scales are used. This relationship is rectilinear at constant respiratory frequency compliance and resistance. The minimum compliance which is theoretically possible can be determined from the chart for a given tidal volume and inspiratory work.

a dominant role in the first breath. Furthermore separation of non-elastic from elastic resistive forces is based on the assumption that the compliance is constant. Although this cannot be proved for the first respiratory movements, the calculated lung compliance will nonetheless at least give information about the average elastic properties of lungs during each breath. Calculated values of compliance from the first three or four breaths as well as from representative breaths later in the different recording periods are shown in Fig. 7a. Calculation of the average pulmonary resistance during the whole respiratory cycle according to Mead does not seem applicable (described in [18]) for the first breaths, since the presence of pronounced hysteresis during these breaths cannot be excluded. The method of calculating the inspiratory pulmonary flow resistance [18] may have less error and has been used for the first three recorded breaths. For the subsequent recording periods the mean pulmonary flow resistance has been calculated according to Mead (Fig. 7b). The inspiratory resistance for the first three breaths showed a wide variation. Most volumes were between 40–120 cm H_2O/l/sec. The normal range for infants is 25–35 cm H_2O/l/sec at the age of some days [16]. However a few cases had

extremely high values. If compared with the values of pulmonary flow resistance obtained from the following recording periods, there is clearly a rapid decrease to a range of 15–60 cm H_2O/l/sec.

The respiratory work required for inspiration of each breath can be calculated from the respiratory loops [18]. This method is suitable for calculations even in the first breaths, since no separation of elastic and frictional forces is necessary. Such calculations have been performed and the results are shown in Fig. 8. The first visible breath does not require increased work in comparison with the second, third or fourth. In three infants, Nos. 65, 64 and 71, the opposite seems to be the case, i.e. low inspiratory work for the first breath.

Discussion

This study has focused on the first breaths because of their probable importance in extra-uterine adaptation. In most infants there is a wide range (12–67 ml) in the volume of the first visible inspiration, considerably larger than the tidal volume in resting newborn infants with established respiration (15–20 ml), but it did not in any instance reach the size of maximal cry (120–160 ml) considered as the vital capacity of a newborn infant [7]. The inspiratory volume of the first breath must imply a reasonable inflation of the lungs when it is considered in relation to the functional residual capacity, which is 80–120 ml at the age of 1–2 days. This observation corresponds well with the results of cineroentgenographic studies [8, 19].

The high negative intra-thoracic pressure change indicates that the first breath is caused by an increase in volume of the surrounding thoracic cage. (Thoracic cage is used here to denote all the walls of the thoracic cavity, the ribs, the intercostal muscles and the diaphragm.) A contraction of the diaphragm seems to be responsible for this pressure fall, since by roentgenologic studies the thorax after the delivery and before the first breath is not compressed [8]. This concept is further strengthened by the present study as well as another study performed in this laboratory [17], in which it has been shown that there is no appreciable negative intrathoracic pressure before the first breath. Cineroentgenographic studies [9, 19] have also demonstrated the diaphragmatic motion. The negative pressure ranged from 10 to 70 cm H_2O. The lungs must overcome three different kinds of counter-acting forces [18]: (1) the increase in elastic tension of the lung tissue itself, (2) the friction due to flow of air and liquid in the respiratory tract, (3) surface tension at the air–fluid interface in the respiratory tract. When compared with conditions later in life, the frictional forces are higher as a result of the narrower airways and because of the amniotic fluid, which has a higher density than air. During initial inflation, air–fluid interface must be created throughout the respiratory tract. Thus the effects of surface tension may be expected to have an increased influence on the mechanics of breathing particularly during the initiation of the first breath. In agreement with this, the respiratory loops from one group of newborn infants showed that an inflation of any magnitude took place only *after* a negative intrathoracic pressure of 20–40 cm H_2O was created. Thus, in the beginning of the

first breath an opening pressure was required, following this, inflation accelerated rapidly This observation agrees with studies of inflation of lungs of still born infants [10] and with Avery & Mead s calculations of the influence of surface tension [1] However in another group of infants the respiratory loops have a shape indicating a low resistance during the inspiration of the first visible breath These observations bring up the question of whether lung-expanding forces rather than pulling (negative intra-pleural pressure) forces exist. The effect of pharyngeal movements [4] or of a capillary erection mechanism [12, 13] cannot be differentiated by the method used in the present study Such forces would not directly influence the intra-esophageal pressure during an active inspiration since the intra-esophageal pressure represents only the pressure difference between the expanding thoracic cage and the pleural surface However from the present findings it seems reasonable to state that contraction of the diaphragm appears to be the principal mechanism for producing the first visible inspiration. The presence of an expiratory volume change immediately preceding the initiation of the first visible breath suggests the possibility of preparatory phenomena for facilitating the inflation of the lungs. This seems particularly attractive since these volume changes in every instance were seen in infants with low inspiratory resistance

The expiratory phase of the first visible breath which always began without pause immediately after the inspiration was usually irregular prolonged and associated with high positive intra thoracic pressure The most probable explanation for this impaired expiration is an obstruction in the upper respiratory tract This appears to correspond to the rhythmical pharyngo-laryngeal closure during the first breaths shown roentgenologically by Bosma & Lind [4] This mechanism prevents air from escaping from the lungs and, during the phase of high positive pressure may further facilitate distribution of air within the lungs. In some instances, the expiration of the first breath occurred fairly rapidly and was followed by an expiratory pause This is also in agreement with Bosma & Lind s observations, since not all their babies showed pharyngeal closure

In each infant the subsequent breaths had a pattern similar to the first There was, however considerable variation between cases There was also a tendency towards less squared loops and decrease of calculated inspiratory pulmonary flow resistance both of which indicate a decrease of resistance There was a wide range of compliance both between and within the cases with no clear change for the first three or four breaths. The actual figures for the mechanical conditions present during the first breaths must be accepted with great reservation. In general however the compliance was one fifth to one-third of that found in infants 1– days of age [10 •1] and the pulmonary flow resistance was at least ?–4 times higher Both measurements indicate that the first three or four breaths require increased respiratory work

In spite of the wide range of tidal volumes, calculated compliance and resistance the estimated efficiency of inspiratory work for the first three breath re-

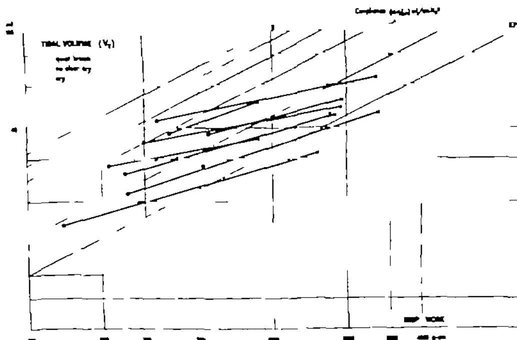


Fig 9 The relationship between tidal volume and required inspiratory work in normal new born infants several days old during quiet breathing and crying (see Fig 8).

corded (V_T^2/resp work) showed a sur prisingly small variation within as well as between the cases. There was no ten- dency for the first breath to require a significantly larger *total* inspiratory work than the following ones. Since calculated work reflects the total work produced by the pulling thoracic cage no differentia tion is possible between work required for overcoming the friction of flow of air and/ or liquid, an increased elastic tension of the lung tissue or the collapsing forces created by surface tension. The relation- ship between these different components may vary between the breaths

In order to estimate whether the first few breaths require an exceptionally high in spiratory effort the same kind of studies and calculations have been performed in 10 healthy infants at an age of several days during quiet breathing and crying (Fig 9) The total inspiratory work as well as its efficiency were found to be of the same magnitude for the first few breaths and a later neonatal cry

It could be expected that the volume recordings would show a continuously increasing end-expiratory level reflecting the establishment of the residual volume However a net volum difference was re corded in only some of the infants and then only during the first visible breath. How ever there are evidences of aerating me chanisms preceding the first visible breath, which may explain the apparent failure to record a residual vol me

Recent studies have shown that the compression of the thorax during the deli

very can cause considerable drainage of amniotic fluid from the respiratory tract. The elastic recoil of the thorax which follows immediately (as the thorax is delivered) results in an inspiratory volume change This mechanism of aerating the respiratory tract seems to be of varying efficiency with gains from 0 up to 40 ml [17].

Compared with the functional residual capacity in newborn infants at an age of 1–2 days with well-established lung function ranging from 80 to 1?0 ml [2 9], such a residual volume will constitute a considerable part of the aeration of the lungs

Bosma & Lind have shown the presence of pharyngeal movements not only during the first breath but before and have pointed out the possibilities of aeration of the lungs by a 'frog breathing mechanism [4] and an elimination of amniotic fluid by swallowing A lung inflation due to "capillary erection has been discussed by Jäykkä [12, 13]

The volume changes, although relatively small, which have been recorded before the first visible breath in the present study may indicate that adaptive respiratory changes may occur between the time of delivery and the initiation of the first breath The absence of recorded residual volume in the first visible breath in some infants seems therefore to have a possible explanation.

In the present study the continuous volume tracings during the first recording period up to one minute after birth did not show any evidence of further significant increase in residual volume However such an increase must occur since measurements by means of a closed circuit helium method at an age of ½–1 hour have shown a functional residual capacity of about 80 ml [9] The continued development of the functional residual capacity after the initial large increment may possibly proceed at such a slow rate as to be missed by the short recording periods. As another possibility it should be realized that an increased aeration occurring simultaneously with absorption of amniotic fluid through the alveoli during the first breaths would not be detected by the method used. It is possible that the high positive intra-thoracic pressure observed during expirations in the first breaths could facilitate absorption. Since lung compliance has been shown to be closely related to the functional residual capacity [5 9] the progressive development of this compartment can be evaluated from the compliance values obtained Calculated from the equation, compliance = 0 05 functional residual capacity [20] the aerated lung volume after the first visible breath (40 ml) should correspond to a lung compliance of 2 ml/cm H_2O and the functional residual capacity at about 1 hour (80 ml) to 4 ml/cm H_2O These estimations are in good agreement with the values obtained in the present study It thus appears that lung compliance calculated from successive recordings may be used for evaluation of the progressive aeration of the lungs even in the early neonatal period The change of lung compliance during this period (see Fig 7) indicates that the aeration of the lungs after the first few breaths progresses rapidly during the first minutes of life and then continues at a slower rate The further development during the first week of neonatal life will be discussed in the following paper of this series [16]

The calculated total ventilation during the first 20 seconds after the first visible breath demonstrates that newborn infants are immediately able to have a ventilation 2–3 times the one at rest later in the neonatal period [6]. This ventilation is efficient to such a degree that the blood-gas values approach the levels found later in the neonatal period within 10–20 minutes after delivery as demonstrated by James [11] and Oliver *et al.* [22]. Furthermore determinations of oxygen consumption and carbon dioxide output at an age of some minutes have indicated a good exchange [14].

The circulatory adaptation (see the review by Stern & Lind [24]) is certainly intimately interrelated with the respiratory one. However in the present investigation no combined circulatory studies were performed.

Summary

1. Respiratory volume changes and intra-esophageal pressure changes have been simultaneously recorded beginning before or during the first breaths in 18 infants.

2. Respiratory adaptive changes for successful extra uterine existence occur rapidly. Some of the features are summarized below.

3. The average air exchange in the first 20 seconds after the first breaths is 2–3 times the resting minute volume observed later in the neonatal period.

4. A residual volume is established in some infants beginning with the first breath. In others this was not recorded and evidence is presented which suggests it may occur prior to the first breath.

5. The total pressure change of the first breath ranged from 40–100 cm H_2O. In succeeding breaths this decreased. Typical pressure volume diagrams ("respiratory loops") are illustrated and their possible significance discussed.

6. During the first few breaths the lung compliance was one fifth to one third and the pulmonary flow resistance _–4 times that found in older neonates.

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Pediatric Clinic
Karolinska sjukhuset
Stockholm 60
S eden

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From the Paediatric Clinic (Head: C. Gyllenswärd), Kronprinsessan Lovisas Barnsjukhus, Stockholm, Sweden

Neurological Signs in a Juvenile Form of Gaucher's Disease

by KARL-MAGNUS HERRLIN and PER OLOF HILLBORG

Gaucher's disease (G.D.) is a lipidosis with deposition of cerebrosides in certain cells of the reticulo-endothelial system (RES). About 300 cases have been published since Ernest Gaucher described his case in 1882. The disease is often familial.

The clinical picture is dominated by enlargement of the spleen and liver, hypersplenism with anaemia, leucopenia and thrombocytopenia, and by changes in the skeleton. In some cases there is also pigmentation in the skin and conjunctivae and signs from the central nervous system. The cerebrosides which are stored in the RES in G.D. contain glucose as the carbohydrate component, while normal cerebrosides contain galactose.

It is usual to distinguish two forms of the disease depending on the age of the patient at the time of onset: an acute infantile form and a chronic adult form.

The *infantile* form appears during the first months of life and leads to death after a period which can extend from a few months to years. There are severe and rapidly worsening cerebral signs with dulling of the intellect, generalized muscular hypertonicity, overactive reflexes, opisthotonos and pseudobulbar phenomena.

In the chronic *adult form*, the symptoms appear later in childhood, during adolescence or in adult life. They are less severe and become slowly chronic in contrast to the development of the infantile form. Neurological signs are slight or completely absent.

Six cases of G.D. are described in this paper whose clinical symptoms developed at the age of 6 months to a year. Progressive cerebral signs appeared at a later stage of the disease in all six children, who are now (1961) between 6 and 20 years of age. Thus these cases cannot be regarded as suffering from the infantile form but are examples of a *juvenile form of G.D.*

Case Material

Hillborg [15] in 1959 described 12 related Swedish children suffering from G.D. Six of them died between the ages of 1 and 2 years. The remaining six, who have previously been discussed in a study of cerebroside content in blood [16], comprise our series. The children belong to four related families (Fig. 1) of Swedish descent, who come from a limited area in northern Sweden.

All the members of families II–IV (Fig. 1) have been neurologically examined, including EEG, but in family I it has only been possible so far to examine patient K. J. and one of her healthy brothers.

After a description of the index patient is carried out and a summary of the most important findings, every member of these

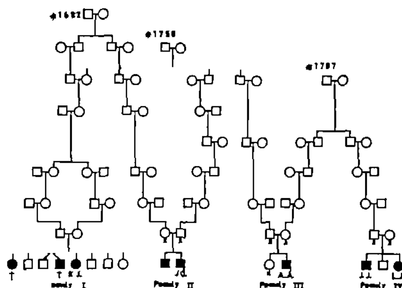


Fig. 1 Family tree ■ = sick boy ● = sick girl † = died of Gaucher' disease X = examined healthy family member

families who has been examined is discussed with particular reference to cerebral sign and EEG findings.

Diagnosis

G D was diagnosed after histopathological examination of the spleen and bone marrow in all 6 cases. Splenectomy was performed on all of them between the ages of 1½ and 1_ years (Table 1) All the spleens contained large round or polygonal cells with a diameter of usually more than 20 microns and with one or several relatively small pyknotic peripherally placed nuclei In four of the spleens the cytoplasm of these cells had the striated or wrinkled structure which is regarded as characteristic of Gaucher cells. In the spleens from Cases S Ö and J Ö who were operated at 1½ years of age the cytoplasm did not have this typical structure Samples of bone marrow from all the children were examined at different ages, before and after splenectomy and all contained morphologically typical Gaucher cells. Specimens from the spleens were stained with ordinary fat stains such as Sudan III, but the cells were only weakly stained PAS staining of bone marrow samples was performed in every case All the specimens showed PAS-positive Gaucher cells.

Chemical analysis of the spleens was carried out in 2 cases (S Ö and J Ö). One spleen (S Ö) was analysed by Professor G Blix at the Department of Biochemistry Uppsala University The sugar concentration was estimated by the anthrone method. From the values obtained the cerebroside content was calculated as being * _ of the wet weight There are no data concerning the water content of the organ but if this is estimated to be about 75 _ the cerebroside content calculated on the dry weight was about 8 _. The content of cholesterol and phos-

pholipids was normal. The other spleen (J Ö) was analysed by Docent L. Svennerholm at the Department of Biochemistry Göteborg University The cerebroside fraction was extracted and hydrolysed, and the sugar content was then estimated, using the orcinol method (Table 2) Neither of the spleens was fixed in formalin. Both had been transported frozen.

In every case the serum acid phosphatase was increased. In the five children between 6 and 14 years of age the value was between 7 15 and 11 41 King–Armstrong units, as against the normal 3.55 ± 1.00 The 20 year old girl had a value of 5 72 units, compared with the normal 2.09 ± 0.44 at that age [17].

The plasma cerebroside content was considerably increased in all cases [16]

Haematological and Physical Examination

The *6 patients* were admitted to a paediatric department on several occasions. Pregnancy delivery birth weight and neonatal period were normal in all cases. They were carefully followed up special ttention being paid to haematological findings, skeletal changes, and signs from the central nervous system before and after splenectomy

The haematological findings were similar in 5 of them. The postoperative reactions of these five children (S Ö J Ö A. Å. J J and L. J) were similar to those following removal of a healthy spleen e g because of rupture Preoperatively they had n anaemia with a Hb value of 43–65 %, a leucopenia of 500–4000 leucocytes/mm and a thrombocytopenia of 60 000–100.000 thrombocytes/mm³ The anaemia was not much affected by the operation. A leucocytosis appeared, which reached its maximum between 6 months and 2 years after the operation, with a value in 4 cases of about 30,000 leucocytes/mm³ The leucocyte count then fell slowly to normal values, but even 4–5 years after operation the values were still about 20 000 leucocytes/mm³ The thrombocyte count rose as early as a few days after operation, to about 500 000/mm³ and then gradually sank during the following months to normal values, which were subsequently maintained. The patient K. J however showed different haematological changes. Splenectomy was not performed until the age of 12 years (Table 1) and preoperatively despite an enormously enlarged and necrotic spleen, she had only a slight anaemia with normal leucocyte and thrombocyte counts Except for a leucocytosis of 26 000/mm³ during the days following splenectomy the blood values have always been and still are normal 8 years later

In all 6 patients, roentgen examination of the skull, spine hip joints and long bones was carried out at the time of splenectomy but no changes were found, though they developed postoperatively within 3½ years

Skin changes in the form of obvious hyperpigmentation were found only in the eldest patient K J Typical pinguecula were not found in any of the patients.

An enlarged liver could be felt in all. It was slightly to moderately enlarged before splenectomy and subsequently increased in size.

The parents and sibl ng were examined

between June and October 1960 They were questioned about previous illnesses especially splenic enlargement anaemia abnormal tendency to bleed, skeletal symptoms such as pain in the extremities limp and fractures, as well as neurological symptoms such as attacks of unconsciousness or fits Possible hospital records were checked. Relatives were examined and special attention was paid to the presence of palpable spleen and liver skin pigmentation and pingueculae Concentration of haemoglobin, red and white cell counts and differential white cell count were calculated. In many cases the thrombocyte count was also estimated. No pathological changes were found. In a number of cases the sternal marrow haptoglobin values and acid phosphatases in the blood were examined. The findings were of interest and will be published by Hillborg [18]

Psychological Examination

The 6 patients were carefully followed up especially after splenectomy and attention was paid to intellectual capacity and possible behaviour disturbances Five are mentally retarded and 2 have marked behaviour disturbances (Table 1)

The parents and siblings all appear to have normal intellectual capacity judging by their development, school achievements and social adjustments. They did not show any noteworthy psychological symptoms either in the history or at the time of examination.

Neurological Examination

The 6 patients were examined between June and July 1960 in the following way plain roentgen examination of the skull, speech tests for dysarthria and aphasia all the 12 cranial nerves including visual acuity and the optic fundi, motility strength and tone in trunk and limb muscles, coordination including Romberg's test, the finger–nose test, the heel-knee test and alternating movements, sensibility in relation to spontaneous paraesthesiae and pain, superficial sensibility to touch pain and temperature joint sense of position in fingers and toes, stereognosis, muscle-stretch reflexes in arms and legs, abdominal and plantar reflexes, the autonomic nervous system e.g skin colour temperature, and moisture intestinal and bladder function In 4 cases the pressure cell and protein contents of the CSF were determined following lumbar puncture

Five of the patients had progressive neurological signs and 3 of them also had epilepsy The optic fundi were normal in all 6 cases.

The parents and siblings were examined between June and October 1960 in a similar way except that no roentgen examination of the skull was made nor were smell, taste vision, optic fundi or CSF examined.

Neurologically they were normal. None had had attacks of epilepsy

EEG Examination

The EEGs were recorded at rest for 15–20 minutes and during 3 minutes hyperventilation Photic stimulation was then performed for 5–10 minutes with 1–30 blue-white flashes per second Chlorided silver pad electrodes were used They were placed according to the 10–20 electrode system (Fig 2) Bipolar lead with six different combinations of electrodes

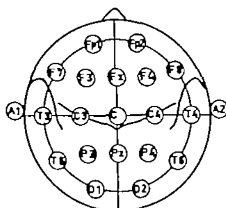


Fig. 2. Position and name of the electrodes.

were used. J Ö was examined with 16 electrodes, but 21 were used for all the others. All were examined while awake with eyes alternately opened and closed. The only one who fell asleep was S. Ö Sedatives were not used. Antiepileptic medication was not discontinued before the recordings. None was fasting

All six children with G.D four of the parents and one of the three healthy siblings were examined at this hospital with an eight-channel Kaiser electroencephalograph, and a Kaiser Universal photostimulator Two of the parents and two of the healthy siblings were examined at the EEG laboratory at the County Hospital in Boden, using an eight-channel Grass electroencephalograph and a Grass photic stimulator model PS-2. Three of the children with G.D were examined at both laboratories with an interval of a few months Recordings were made between March and October 1960

All the EEG recordings have been assessed by us. *The 6 patients all* had pathological EEGs to a greater or a lesser degree *The parents and siblings all* had normal EEGs except for one sibling with suspected abnormality

Case Reports

Family I (Fig 1)

Two children, a daughter and a son, died in 1937 and 1940 at the ages of 3 and 2 years respectively Both had typical clinical signs of G.D. The girl spleen weighed 1170

TABLE 1

- slight, + + – moderate + + + – severe grade of signs.

Pat.	Age at splenect (yrs) Weight of spleen (g)	Age at investig 1960 (yrs)	IQ	Cerebral signs: Behaviour disturb.	Motility disturb.	Epilepsy	EEG
K. J	12 3100	20	73–74	+	+	—	+
S. Ö	1½ 335	8	71	+ +	+ +	+ + +	+ + +
J Ö	1½ 440	6	61	+	+ + +	—	+ +
A. A.	1½ 430	14	113–79–66	+ + +	+ +	+	+ + +
J J	7 1300	13	45	+ + +	+	+ + +	+ + +
L. J	3 700	9	88	—	—	—	+ +

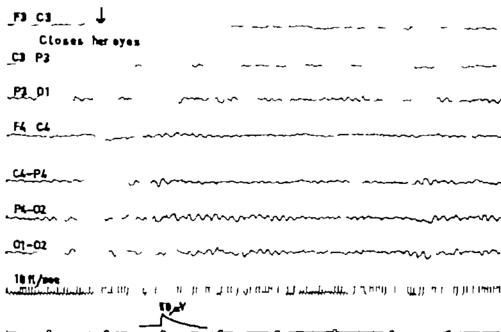


Fig. 3. EEG from K. J (aged 20) At rest and during photic stimulation, with open and closed eyes, 6–7/sec. waves dominated. N discharges. Little effect from hyperventilation. In all EEGs the interval between the time marks is 1 sec.

g and showed a typical histological picture of G D The parents and their six living children all appear to be healthy except for K. J

Son Born 1933. Post office worker H has always been healthy EEG was normal.

Daughter with G D (K. J). Born 1940 At 1 year of age splenomegaly was found at routin examination. Except for a tendency to upper respiratory tract infections she was healthy during the following years. At I years she was admitted to a paediatric department because of increasing pain and a feeling of hea iness in the abdomen. A mild anaemia was found, but no leucopenia or thrombocytopenia. The spleen was removed It weighed 3100 g and was almost complet ly necrotic. At the age of 13 years an increasing kyphosis appeared in the lower thoracic spine Roentgen examination of the skeleton at 16 years of ge showed a collapse of the vertebrae Th 9–11 kyphosis with an angle f 90 and widened femoral metaphyses. Her intellect has always appeared rather poor but she has continued for 6 years in school with moderate records. Her intellectual capacity has recently deteriorated and she has become increasingly indolent and unable to concentrate. She was unable to complete her training as a seamstress t 17 years of age She was tested on the Terman–Merrill scale at 17 years of age (I.Q 72) and at 20 years of age (I Q 74) She has not had any epileptic attacks.

When she was examined at the age of 20 years, an bvious yellow brown hyperpig mentation f the face was found and there was a sharp boundary with kin not ex posed to the sun Neurologically she wa normal, except for an abduction defect of 20 in both eyes, generally jerky and stiff movements of the eyes and ymmetrical hyperkinesis of the face in the form of grimaces and blinking Her vision in both eyes was 0.6 after correction of a moderat

myopia and astigmatism. The CSF contained 97.5 mg per 100 ml total protein but was otherwise normal. The high protein content was probably due to a partial CSF block caused by her kyphosis. The EEG showed a slow rhythm for her age (Fig. 3).

Family II (Fig 1)

Father Born 1927 Baker H has always been healthy EEG was normal.

Mother Born 1932. Housewife She has always been healthy EEG was normal.

Son with G D (S Ö). Born 1952. On routine medical examination t 7 months f age splenomegaly was found. He was ad mitted to a children department t the age f 1 year Anaemia, leucopenia and thrombocytopenia, enlarged spleen and liver and petechiae in the skin were found. At 1½ years f age splenectomy was performed. The spleen weighed 365 g At 3 years of age he began limping with his left leg Roentgen examination of the skeleton at the age of 5 showed changes in the left femoral head similar t Perthe's disease, and widened femoral metaphyses. Like his younger brother he has become more and more irritable, obstinat and impatient during recent years. His intellectual capacity has diminished. He was considered too immature for school t 7 years f age At 8 years he was tested on the Terman–Merrill scale (I.Q 71). From the age f 4 years his movements have been stiff and lumsy Since the age of 6 he has had minor seizures and psychomotor ttacks of temporal lobe type and grand mal seizures, which have all increased in frequency and severity Mebaral and diphenyl hydant in have not had any appreciable effect

H was examined at the age f 8. He was small and very thin, with a moderat thoracic kyphosis but without roentgen changes in the vertebrae Neurologically he had lear abduction defect in both eyes, jerky eye movements, tics of the left side of the mouth and generalised stiff and clumsy movements. H had a certain amount of trismus and opened his mouth with difficulty Two EEGs recorded with an interval of month showed frequent abnormal dis charges, which were more pronounced in the latter (Fig 4).

Son with G D. (J Ö) Born 1954. At months routine examination showed anaemia, leucopenia, thrombocytopenia, enlarged spleen and liver At the age of 1 year he developed a tendency to bleed. He was ad mitted to a paediatric department. Splenectomy was carried out at the age of 1½ years. The spleen weighed 440 g At 2½ years a thoracic kyphosis of increasing severity appeared. Roentgen examination f the skeleton at the age of 4 showed no changes in the vertebrae but widened femoral metaphyses and suspected changes in the left femoral head. The mother had noticed increasing mental retardation. He was tested on the Terman–Merrill scale at 6½ (I Q 61) At the age of 2 he developed convergent strabismus f both eyes, difficulty in opening the mouth and swallowing, a cramp-like cough with inspiratory stridor when nervous and a generalised stiffness f movement All the signs have progressively increased. The mother has not noticed epileptic attacks.

H was examined at the age of 6½ He was strikingly small and very thin for his age with poorly developed muscles. Neurologically there was defective eye movement with pronounced convergent strabismus, inability to abduct the eyes beyond the midline and impaired movement upwards and downwards. H could not actively open his mouth more than 1 cm. All movement were stiff and clumsy H could only mount one flight of stairs with great difficulty H had a mild tremor and dysmetria in the hands. Two EEGs recorded with an interval of months showed generalised episodes with low waves of high amplitude (Fig 5).

Family III (Fig 1)

Father Born 1910. Merchant H has always been healthy EEG was normal.

Mother Born 1911 Housewife She suffers from migraine but has otherwise been healthy EEG was normal.

Daughter Born 1940 Clerk. She wa healthy EEG was normal.

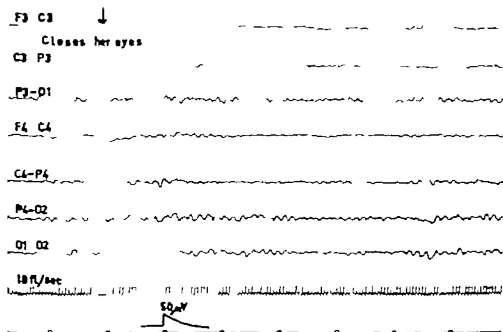


Fig. 3. EEG from K. J (aged 20). At rest and during photic stimulation, with open and closed eyes, 6–7/sec. waves dominated. N discharges. Little effect from hyperventilation. I all EEGs the interval between the time marks is 1 sec.

g and showed a typical histological picture of G D The parents and their six living children all appear to be healthy except for K. J

Son Born 1933. Post ffice worker He has always been healthy EEG was normal

Daughter with G D (K. J) Born 1940 At 1 year of age splenomegaly was found at routine examination. Except for a tendency to upper respiratory tract infections she was healthy during the following years. At 1 *years she was admitted to a paediatric* department because of increasing pain and a feeling of hea ness in the abdomen. A mild anaemia was found, but no leucopenia or thrombocytopenia. The spleen was removed It weighed 3100 g and was almost completely necrotic. At the age of 13 years an increasing kyphosis appeared in the lower thoracic spine Roentgen examination of the skeleton at 16 years of age showed a collapse f the vertebrae Th 9–11 kyphosis with an angle of 90 and widened femoral metaphyses. Her intellect has always appeared rather poor but she has continued for 0 years in school with moderate records. Her intellectual capacity has recently deteriorated and she has become increasingly indolent and unable to concentrate She was unable to complet her training as a seamstress at 17 years of age She was tested on the Terman-Merrill scale at 17 years of age (I.Q 7*) and t 20 years of age (I.Q 74). She has not had any *epileptic attacks.*

When she was examined at the age of *0 years, an obvious yellow-brown hyperpig ment tion f the face was found and there wa a sharp boundary with skin not ex posed to the sun. Neurologically she was normal, except for an abduction defect of *0° in both eyes, generally jerky and stiff movements of the eyes and symmetrical hyperkinesis of the face in the form of grimaces and blinking. Her vision in both eyes was 0 6 fter correction of a moderat

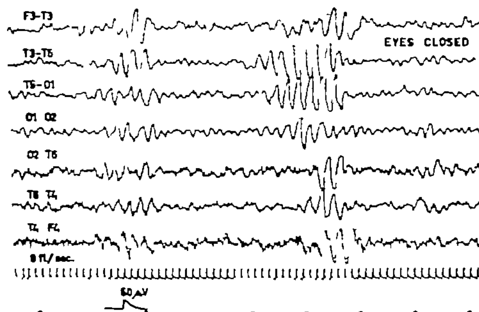


Fig. 5. EEG from J Ö. (aged 8½). During photic stimulation numerous bilateral episodes with enlarged 4–5/sec waves were recorded at different flicker frequencies. At rest isolated similar episodes were seen. Background activity with 6–7/sec. waves. He could not hyperventilate.

was very thin and muscularly weak with a rather pronounced thoracic kyphosis but with no roentgen changes in the vertebrae Neurologically there was a mild bduction weakness in both eyes, tic-like movements of the head t the left, generalised stiff and clumsy movements, difficulty in opening the mouth, moderate tremor of the fingers and dysmetria in the hands. H had brisk ankle jerks but no foot clonus, hyperreflexia, muscular hypertonicity or Babinski' phenomenon. The EEG was highly abnormal with variable epileptic discharges from the whole cortex (Fig 6)

Family IV (Fig 1)

Father Born 1923. Lorry driver H has always been healthy EEG was normal.

Mother Born 1925. She has always been healthy EEG was normal.

Son with G D (J J). Born 1947 From the age of 6 months the abdomen increased in size Otherwise he seemed well until the age of 5½ when medical advice was sought because of his pallor and tiredness. H was admitted t a paediatric department, where anaemia, leucopenia and thrombocytopenia were found. The spleen could be felt filling the whole of the left side of the abdomen down t the symphysis pubis. Splenectomy was performed at the age of 7 years. The spleen weighed 1300 g At the age of 10 he began limping with the left leg Roentgen examina tion showed necrosis in the left femoral head as in Perthe disease and widened femoral metaphyses. His intellectual development was considered to be normal when he began school at 8. During the next few years a mental change developed progressively with restlessness, reduced ability to concentrat nagging and violent outbursts of temper At 12 he was transferred a day school

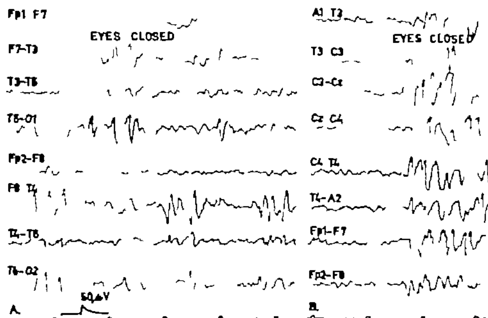


Fig 6. EEG from A. Å. (aged 14½) A Mono-, bi and triphasic spikes in one or the other hemisphere and with temporal predominance. B Abrupt change from normal rhythm dominated by 8/sec activity to generalised abnormality appearing during 5–10 sec. episodes. In addition short generalised paroxysms with irregular spike-and wave activity appeared. Photic stimulation t 8 flashes/sec. produced clouding of consciousness and generalised convulsions. Hyperventilation did not increase the bnormality

for mentally backward children. At 13 he was *tested on the Terman–Merrill scale* (I Q 55) When he was 9 years old, short confusional episodes appeared with stereotyped hand movements. At 10 psychomotor seizures appeared *with visual hallucinations* as the aura, meaningless motor and verbal *automatisms, confusion and amnesia. At 11* he developed major attacks with generalised convulsions and unconsciousness. *All three* kinds of attack have increased in severity and *frequency to as much as a few minor seizures* every day and some psychomotor or major attacks every week. *H has been treated* with mysoline without any obvious effect

On examination at 13½ he was rather small for his age and very thin, with a moderat thoracic kyphosis. *Neurologically he suffered* from generalised stiffness and jerky movements which were most noticeable in the eyeballs, but otherwise *nothing of note* The CSF was normal. Two EEGs recorded at 12½ and 13 years of age showed *similar pathological* changes (Fig 7).

Son Born 1948. He was healthy *with normal* development. During hyperventilation *the EEG showed somewhat enlarged sharp* wave-shaped potentials from the left temporal *region, but otherwise it was normal.*

Daughter with G D (L. J) Born 1951 *At 1 year increase in the size of the* abdomen wa noticed. The child was admitted t *paediatric department t the go f —* Splenomegaly anaemia, leucopenia and *thrombocytopenia were found* The spleen was f lt somewhat below the plane of the *umbilicus. Splenectomy wa performed t* the ge f 2 years. The spleen weighed 700

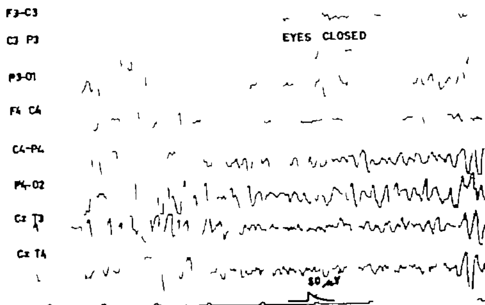


Fig. 7 EEG from J J (aged 13½). High-amplitude 3–4/sec. waves with varying predominance in different areas against background of lightly irregular rhythm with 7–8/sec waves. Hyperventilation and photic stimulation increased the dysrhythmia. No distinct paroxysms.

g. At 4 she began to complain of pain in the legs during physical exertion. Roentgen examination at the age of 8 showed normal hip joints but widened femoral metaphyses. She has not changed mentally and is in the normal class. In school she was tested on the Terman–Merrill scale at the age of 9½ years (I Q 84). The mother is of the opinion that since the age of 8 the child has sometimes been stiff in her movements and has had difficulty in keeping her balance. No epileptic attacks have been noticed.

On examination at the age of 9½ her condition was normal with the exception of slight thoracic kyphosis. Her neurological findings, including CSF were normal. The EEG was pathological with paroxysmal abnormalities during photic stimulation (Fig. 8)

Comments

The six children with G D had splenomegaly as early as 6 months to 1 year of age. Anaemia, leucopenia and thrombocytopenia developed in five of them during the next few years, while one had only mild anaemia. The liver slowly increased in size. Skeletal changes and cerebral signs developed after splenectomy which was performed between the ages of 1½ and 1 years (Table 1). Typical Gaucher cells were found in all the children. Chemical analysis of the spleens from S Ö and J Ö showed pathological quantities of cerebrosides containing glucose which i considered to be specific for G D On the

sometimes surrounded by Gaucher cells, and that similar cells can be found in the adventitia of the vascular wall. Accumulation of such cells in and round the adventitia of the small and med um-sized vessels of the brain has since been observed by Debré *et al.* [8], Brante & Gertzén [4] and Norman *et al.* [1] According to Barlow [1], these changes in the cerebral vessels are important. H found that these cells definitely appear to be Gaucher cells. They were seen in the walls of the small subcortical vessels of the white matter especially in the temporal and occipital lobes. Diezel [10] maintained that these adventitial cells contain stored cerebrosides and that they may be the cause of the cerebral signs. Theoretically we assume that the vascular changes may impair vascular dilatation when the oxygen demand in the brain is increased, prevent normal diffusion or facilitate thrombosis.

Pick [3, 24], in some of his works on G D., referred to investigations carried out on phagocytosis of iron pigment and fat in infants. These investigations indicat that phagocytic RES cells in organs other than the spleen, liver bone marrow and lymph glands lose their phagocytic ability t the age of about 1 year According to Pick, this explains why G D in infants progresses so violently and involves so many more organs than when the disease appears in later years.

Bird [ ] described the post mortem findings in an 11 year ld boy with presumed G D whose cerebral signs, which were similar to those of our 6 cases ppeared t the age of years. H found swollen or degenerated ganglion cells in the cerebral cortex, basal ganglia, brain stem and cerebell m. He compared the findings with the histological changes in three brains from cases with amaurotic family idiocy Bird thought that lipid infiltration with its accompanying degeneration of th ganglion cells, was the common histological finding in all 4 cases. On this basis he postulated that both diseases, as well as Niemann–Pick's disease are examples f neuronal lipidoses and that the primary lesion is to be found in the nerve cells. Brain [3] described a similar case

Later however Brant maintained that these cases probably did not have G D but some other *kind of lipidosis* [5]. In this context it may be mentioned that in 193 Reese & Kato [5] described three *siblings* with G D., two of whom had progressive cerebral signs in adolescence. The diagnosis of G.D can hardly be doubted, considering the description of the appearance of the splenic cells, stored with lipids, and the type and location f the changes in the skeleton, but unfortunately no chemical analysis of the spleen was carried out.

In our 6 cases the cerebral signs consisted of (Table 1)

(1) Mental retardation in 5 cases, with an I Q of 74 or less.

(2) Obvious behaviour disorders, psychotic in type and progressive dementia in 2 (A Å. and J J)

(3) Neurological signs in 5 similar and slowly progressive in type appearing as a generalised stiffness, clumsy and jerky movements with defective coordination, particularly noticeable in eye movements, and impaired ability to abduct the eyes. In addition, in 3 of them (S Ö J Ö and A Å.) there was trismus in J Ö dysphagia and laryngeal stridor as well and in 3 (K. J., S Ö and A Å) tic like hyperkinesis of the face

(4) Epilepsy in 3 with especially confusional episodes and psychomotor attacks of temporal lobe type

(5) Pathological EEG of varying severity in all 6

It is unlikely that the accumulation of cerebral signs in these six children is due to chance Nor is it likely that they are caused by any hereditary disease other than G D If this were so, similar cerebral signs without the presence of G D would

have occurred in some of the relatives, but this was not the case

The mental and neurological signs point to a diffuse progressive encephalopathy To some extent they resemble the cerebral symptoms of the infantile form of G D but they are less pronounced and their progress is less sudden.

The EEG findings also indicate a general cerebral dysfunction. There were no distinct focal findings or discharges with regular pattern. The EEG from K. J (20 year old girl without epilepsy) was charac terized only by a rhythm which was slow for her age (Fig 3). The EEGs from both the other children without epilepsy (J Ö and L. J) showed at rest a normal or somewhat irregular rhythm, but during photic stimulation J Ö had bilateral paroxysmal episodes with enlarged slow waves (Fig 5) and L. J had general spike-and wave discharges (Fig 8) Such parox ysms during photic stimulation are un usual in children without clinical signs of cerebral dysfunction [14]. They are possibly caused by a neuronal hyperexcitabil ity with the result that the repetitive im pulses from cortical or subcortical centres in the visual pathways produce abnormal discharges within the brain stem from which the cortex of both hemispheres is activated via thalamo-cortical connec tions [1]. The EEGs from the three children with epilepsy (S. Ö A Å and J J) were characterized at rest by nu merous discharges with spikes, sharp waves and slow waves which appeared at irregular intervals, changing in form and site during the recording (Figs. 4 6 and 7) Similar EEG findings have been described in 12 children with non-specific forms of "cerebral lipidosis [6]. They were all under 9 years of age with epilepsy and mental retardation. The background ac tivity in the EEGs from these 12 children consisted of slow irregular waves of high amplitude while the basic rhythms of our three children, who had similar spon taneous discharges, were normal or only slightly irregular This dissimilarity between the EEG findings in the 1* children mentioned above and those of our children with G D may be due to a difference in the type of degenerative cerebral processes involved. In this context it is worth mentioning a child with Tay-Sach s disease and epilepsy who was carefully studied during the course of the disease [*0]. In the first stages of the illness the EEG showed spontaneous discharges, similar to those in our children with epi lepsy (S Ö., A. Å. and J J) who have the most pronounced mental and neurological symptoms of our six children (Table I) In view of these facts it is likely that the EEG findings in the cerebral lipidoses depend more on the stage of the cerebral process than on the kind of lipidosis In the three children mentioned the EEG pattern varied between a normal or nearly normal rhythm and cortical discharges of dif fering localisation (Figs 4 6 and 7) In their EEGs there were also paroxysmal episodes with a generalised irregular abnormality from the whole cortex (Figs. 4 and 6) This abnormality was possibly elicited within subcortical structures in the brain stem. The variable hyperex cit bility in the cortex may be caused by vascular changes, which give rise to local relative hypoxemia

The histological findings in the brain in the infantile form of G D which have been described in the literature were

usually degenerative changes in the gang lion cells of the cerebral cortex, basal ganglia, mesencephalon and cerebellum [1 8 13 21 22 26 and 29] The cortical changes in the cerebrum have sometimes been most pronounced occipitally and temporally In the basal ganglia the thala mus and pallidum have been most changed, in the midbrain the red nucleus and substantia nigra and in the cerebellum the dentate nucleus. The above-mentioned histological findings in the infantile form are certainly consistent with the cerebral signs in this form of the disease and even with the mental, neurological and electroencephalographic findings in our six children.

The enzyme defect which causes G D is still unknown. The substances which are stored in the other sphingolipidoses, i.e Niemann–Pick s disease amaurotic family idiocy and gargoylism chemically re semble cerebrosides It is therefore likely that these sphingolipidoses are due to an enzyme defect similar to G D Diezel [11] has pointed out that the metabolic disturbances within a diseased group may show certain variations from one organ to another as well as from one case to another It is probable that different cases of G D (as previously defined) will present somewhat varying clinical pictures depending on minor differences in the metabolic disorder It is possible as a result that those cases with a uniform clini cal picture, which we have described in some related families from northern Sweden, have a variant of the classical form of G D and that this variant is partly characterized by the cerebral signs

There are skeletal changes in all our six children. They appeared early and in all cases within 3½ years after splenectomy independent of the age at which it was performed. This age varied between 1½ and 12 years (Table 1) Thus it looks as if loss of the spleen accelerated the appear ance of skeletal changes. At splenectomy the body s largest reservoir of RES cells is removed. So it seems natural to assume that the cerebrosides circulating in the blood after splenectomy are mainly stored in the liver and bone marrow which causes enlargment of the liver and increasing skeletal changes By analogy the cerebral signs may be explained by vascular changes arising from the deposition of cerebrosides in the cells of the adventitia. In consequence it is possible that splenectomy performed early in five of these six children, was a contributory cause in the development of cerebral signs

Summary

The occurrence of progressive cerebral symptoms is described in a juvenile form of Gaucher s disease in a clinical series assessed uniformly This series is composed of six persons, still living between the ages of 6 and 20 belonging to four related families, who all come from a limited area in northern Sweden All 6 patients have shown the same clinical histopathological and histochemical findings, and all have undergone splenectomy Two spleens were chemically analysed. Their lipid content was typical of Gaucher s disease All cases developed skeletal changes within 3½ years of splenectomy

The cerebral signs consisted of mental retardation in 5 cases, psychotic behaviour disorders in 2 cases generalised rigidity and jerky movement in 5 epilepsy in 3 and

a pathological EEG in them all. Similar signs were not found among the children's relatives.

The progressive mental and neurological symptoms indicate a diffuse, progressive encephalopathy which affects the cortical and subcortical grey matter. The authors think it likely that the cerebral signs have a vascular origin and are caused by deposition of cerebrosides in the adventitial cells of the cerebral blood vessels. Similar cerebral changes have been described in the infantile form of Gaucher's disease. Splenectomy performed at an early age may have been a provocative factor in the development of these hypothetical vascular changes and of the early skeletal changes.

Addendum

After the manuscript of this paper was accepted for publication we have noticed a report of a case of juvenile Gaucher's disease with neurological signs of the same type as in our cases. Maloney, A. F. and Cumings, J. N.: A case of juvenile Gaucher's disease with intraneuronal lipid storage. J Neurol Neurosurg Psychiat 23: 207, 1960.

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Kronprinsessan Lovisas Barnsjukhus
Polhemsgatan 30
Stockholm K
Sweden

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From the Paediatric Clinic at Kronprinsessan Lovisas Barnsjukhus, Stockholm, the Royal Schools of Dentistry Stockholm and Umeå, the National Bacteriological Laboratory Stockholm, and Epidemisjukhuset Eskilstuna

Dental Development in Children Following Maternal Rubella

by ROLF LUNDSTRÖM, LENNART LYSELL *and* NILS BERGHAGEN

The teratogenic effect of rubella in early pregnancy has been confirmed in numerous reports published since the first communication by Gregg [6].

The organs most often affected are the eyes, ears, and heart. Also disorders of dental development have been described by several authors, as aplasia of teeth delayed *eruption of teeth*, enamel hypoplasia, and a high incidence of caries [1–4 11–14].

Material

A prospective study of children with histories of maternal rubella was started by Lundström [7].

1 A follow up at the age of approx. one to three years included, among other examinations, also information on the number of teeth and dental abnormalities observed. The examination was performed by physicians, in nearly one-half of the cases by paediatricians, and comprised approx. 98 per cent of the cases registered at birth. As seen in Table 1, information on 979 children with histories of maternal rubella obtained at delivery and on 639 controls sampled at random was collected. Rubella had occurred within the first four months of pregnancy in 550 cases and in 429 in the fifth or following months. Data on birth weight height at birth and circumference of the head at follow-up examination had also been collected.

2 An ophthalmologic examination of the aforementioned children living in the Stockholm area was made at Södersjukhuset Stockholm, by Lundström & Boström [8]. At the same time a dental examination was made, comprising children with histories of maternal rubella, of exposure without contracting rubella, and controls. Only some parents were cooperative. However 18 children of women with maternal rubella, 43 whose mothers had been exposed in pregnancy but had not contracted manifest rubella, and 5 controls were examined at one to three years of age

3 *A further investigation of the children* supposed to live in Stockholm comprised 118 children who were summoned for dental examination at the Royal School of Dentistry in Stockholm. Seventy-six had histories of maternal rubella and 42 were controls, all born in 1951 Fifty-five rubella children were examined, of the remainder 4 had moved to distant places, 12 to addresses not known (letters were returned) and 5 did not reply (letters not returned).

Method

1 The dental examination of the children in the first part of the study recorded the teeth present and reported obvious abnormalities

This part consisted of full dental exa

TABLE 1 *Number of teeth and age at examination in relation to time of maternal rubella compared with the controls*

Rubella in month of pregnancy — I IV

Age at exami nation, months	12	13–18	19–24	25–30	31–35	>36
No. of teeth						
0 4	18	33	1			
5 9	22	144	6			
10 11	1	29	5			
12–13		69	21			
14 15		4	19	2		1
16 17		13	77	40		1
18 19			7	1	1	
20			6	17	15	7
Children examined	41	292	15_	40	16	9
Mean no. of teeth	4.90	8.61	14.00	17.94	19.91	19.00

Total no. 550

Rubella in month of pregnancy — V X

Age at exami nation, months	12	13–18	19–24	25–30	31–35	>36
No. of teeth						
0 4	7	10				
5 9	4	96	1	3		
10 11		46	1			
12–13		74	12	1		
14 15		14	9			
16 17		37	30	9	1	
18 19			4	5		
20		3	13	19	10	12
Children examined	11	290	78	37	11	12
Mean no. of teeth	3.82	10.82	16.10	17.69	19.68	20.00

Total no. 4?9

Controls

Age at exami nation, months	12	13–18	19–24	25–30	31–35	>36
No. of teeth						
0 4	10	19				
5 9	19	155	3			
10 11		36	4			
12–13	1	89	25	1		
14 15		18	17	1		
16 17		38	70	40	2	1
18 19		1	8	11	3	1
20		2	16	23	23	16
Children examined	30	258	141	65	27	18
Mean no. of teeth	5.53	9.94	15.66	17.98	19.63	19.72

Total no. 639

mination by a dentist and included a history of sucking (finger nipple, etc.), number of teeth at examination, and gingiva.

2. This part, also performed by dentists, comprised questions concerning age t eruption of the first deciduous tooth and on sucking habits, examination for caries and enamel defects, registration of the occlusion as regards the sagittal and transver sal relation between maxilla and mandible, estimation by eye of deep overbite proclined maxillary incisors, obvious crowding or overspacing in the dental arches, obvious deviation of the single tooth, and finally appearance of the gingiva (normal, inflamed and/or enlarged).

Hypoplasia of enamel was defined as an obvious defect of the substance without caries. Aplasia of tooth was registered only when confirmed by X-ray at time for normal eruption.

Results

1 *Follow-up of Children n the Country-wide Study*

Three cases were reported with notable dental defects. One child whose mother had rubella in the second month had fused lower medial incisors. One child seemed to be deficient of the germ of an incisor (not confirmed by X ray) the mother had been in contact with rubella without contracting the disease in the fourth month of pregnancy as had the mother of one child, reported with a marked malocclusion of teeth, not specified.

Table 1 shows number of teeth and age at examination. The number of teeth present was recorded in 1618 (550 + 429 + 639) children As a whole one got the impression that the children with histories of rubella in the first four months had a lower mean number of teeth than the other groups. As the age at xamination of the children varied, the age when the majority of the children were examined was chosen for comparison, namely 13–18 months (approx. 15 months Table *) In 29* children following maternal rubella in the first four months of pregnancy the average number of teeth was 8 6, in 280 children following maternal rubella in the fifth and following months 10 6 and in 358 con trols 9.9 The difference between the means of the early rubella group and the other groups was considerable and significant ($P < 0\ 02$) and could not be correla ted with birth weight height at birth nor with the head circumference at exa mination.

TABLE 2 *Mean no of erupted teeth at approx 15 months (13–18 months) of age.*

	Rubella in month of pregnancy					
	I IV		V X		Controls	
	Mean no. of teeth	No. of in dividuals	Mean no. of teeth	No. of in dividuals	Mean no. of teeth	No. of in-dividuals
Total	8.6	292	10.6	280	9 9	358
Birthweight > 2.100 kg	8.8	215	10.7	49	10.1	309
Height at birth < 49 cm	8.3	80	9.3	43	8.8	64
Height at birth > 50 cm	8.7	212	10 9	235	10.2	294
Head circumference < normal	7.9	44	10.7	17	9.3	20
Head circumference > normal	8.7	248	10.6	263	10.0	338

2 Dental Examination at One to Three Years of Age

Brownish pits in upper incisors were observed in one child with a history of maternal rubella in the fourth month. No significant pathological findings were observed in the other children, no differences being observed as to sucking habits, number of teeth at examination, and condition of the gingiva.

3 Dental Examination of Children at About Five Years of Age

The average age at examination was 4 70 4.78 and 4 73 years in the different groups (Table 3)

(a) Age at eruption of first deciduous tooth

The children with histories of maternal rubella in the first four months were on an average 1 month older than the children with maternal rubella later in pregnancy and the controls when the first tooth appeared according to statements by the mothers. This difference is, however not convincing as the number of observations is small.

(b) Incidence of carious teeth

No tendency to difference between the means of missing and carious teeth in the groups of early maternal rubella late maternal rubella and controls was found. In the rubella groups nine cases were free from caries, in the control group five

(c) Enamel hypoplasia and aplasia of teeth

Neither enamel hypoplasia nor aplasia of teeth was observed in any of these children.

(d) Gingiva

Local inflammation of gingiva was observed in some cases presumably due to buccal cavities of teeth. Five cases in the rubella groups and three in the control showed this disorder Slightly hyperplastic gingiva in two cases of the rubella groups was also registered

(e) Sucking habits

Histories of sucking habits especially thumb-sucking were reported for about one-half of the children in each group.

(f) Incidence of malocclusions

Normal occlusion was found in 1 cases among the rubella children and in 13 controls. No differences were observed concerning the incidence of malocclusion. Postnormal occlusion was observed ten times in the rubella groups and six times among the control usually in combination

TABLE 3 *Dental examination of 55 children with histories of maternal rubella and of 33 controls living in Stockholm Children following maternal rubella in the first four months were on an average one month older than those of the other groups at eruption of first deciduous tooth The differences as regards caries incidence and missing teeth are not convincing*

	Rubella in month of pregnancy I IV	Rubella in month of pregnancy V X	Controls
No. of children	35	20	33
Age at examination, average in years	4.70	4.78	4.73
Age at eruption of 1st deciduous tooth (by history) average in months	7	6.5	6.
Carious (filled) teeth, mean no.	6.9	7	6 0
Non-carious teeth, mean no.	12.6	12.0	12.5
Missing teeth, mean no.	0.5	0.3	0.4

with deep overbite Crowded teeth occurred in seven cases of the rubella groups and in two control cases. Proclination of upper incisors was seen in four rubella children and two controls. Single cases of pre nor mal occlusion, lateral cross-bite and devia tion of a single tooth were also observed.

Discussion

The first step of this investigation comprised children of a country wide study born subsequent to an epidemic of rubella in Sweden in 1950–51 based on inquiries of approx. 100 000 pregnant women who were asked when admitted to maternity hospitals if they had had rubella during actual pregnancy Approx. 1000 women had answered in the affirmative Their child ren and matched controls have been the subjects of a follow up study

A the first part of the present study is based on observations by physicians, it was to be expected that dental abnor malities other than delayed eruption of deciduous teeth would not be reported to any great extent Thus only three cases of obvious abnormalities, comprising one case of fused lower medial incisors, one case of a missing incisor nd one case with a pronounced not specified maloc clusion were reported Only the case of fused incisors had a history of maternal rubella the other two had histories of con tact without contracting the disease in the fourth month of pregnancy These single observations are inconclusive

However the dental development ex pressed in number of erupted teeth among children aged one to three years sug gested that difference between the group with histories of maternal rubella in the first four months and the control group existed. The group with histories of maternal rubella in the fifth and fol lowing months did not show any difference

The difference amounting to 1.3 teeth was significant ($P < 0.02$) in the children aged approx. 15 months. It is known that immaturity at birth is more common among children with histories of early maternal rubella than among children taken at random [9], and this could possibly explain the delayed dentition in this group. However as birth weight and height at birth do not influence the num ber of teeth another factor seems to be responsible

Subnormal head circumference at one to three years of age occurs more often among the children of mothers with rubella in the first four months of pregnancy than among the controls [10] A comparison of the den tition regarding this factor shows that the delay of eruption of teeth is somewhat more marked among the rubella children, but the difference is the same regardless of the children having a normal or subnormal head circumference

The material from the dental examina tion seems to be too small to allow any conclusions However comparing the histories of eruption of first tooth of the rubella children compared with the controls a tendency to one month delay was noted for the early rubella group, which was not significant but is supported by the findings in the country wide investiga tion.

Hypoplasia of enamel and a more mar ked incidence of caries was not observed. It should be kept in mind that as a delay of eruption exists among the rubella children, their teeth have been exposed to

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TABLE 3. *Dental examination of 55 children with histories of maternal rubella and of 33 controls living in Stockholm. Children following maternal rubella in the first four months were on an average one month older than those of the other groups at eruption of first deciduous tooth. The differences as regards caries incidence and missing teeth are not convincing*

	Rubella in month of pregnancy		Controls
	I–IV	V–X	
No. of children	35	20	33
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Age at eruption of 1st deciduous tooth (by history) average in months	7	6.8	6.7
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No tendency to difference between the means of missing and carious teeth in the groups of early maternal rubella, late maternal rubella and controls was found. In the rubella groups nine cases were free from caries, in the control group five.

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Department of Pediatrics, New York University Medical Center New York 16, N Y

The Incidence of External Hernias in Premature Infants[1]

by S. ZOE WALSH

The incidence of both umbilical and inguinal hernias in premature infants is stated to be high, and is thought to be due to the poor development of muscle and fascia [1 –] However relatively few studies on the frequency of external hernia in prematurely born infants have been re ported.

Hess stated that more than 70 % of premature infants developed umbilical hernias of sufficient size t require early attention [4] Woods also reported a high incidence of umbilical hernias in premature infants. Very few of the infants included in her study however weighed less than 2000 g [9].

Ylppö reported that the incidence of in guinal as well as umbilical hernia was higher in premature than in full term infants [10]. Ramber & Goldberg failed to confirm Ylppö s findings in regard to inguinal hernia [8].

Hernias are usually detected during the first 6 months of life Repeated observations at frequent intervals for 6 to 1* months are needed to determine ac curately the frequency of umbilical and inguinal hernia. The data presented in this paper are based on 82 healthy premature infants weighing less than 2000 g

This study was supported by grant from the New York Heart Association and the Burroughs Wellcome Company

Other data on these infants will be published shortly

Material and Methods

Eighty-two healthy premature infants weighing less than 2000 g t birth were divided into two groups, according to weight. Group I included infants weighing less than 1500 g, and Group II those weighing more than 1500 g The two groups were not comparable in regard t race or sex.

All the infants were examined during the first week of life. Regular follow-up observations were mad whenever possible at the following ages: 1 month, 1 to 3 months, 3 to 6 months 6 to 12 months, and more than 12 months. Thirty of the 82 infant were ex amined on five occasions. Two were seen only twice. On each visit, the infant was carefully examined and the mother questioned as to whether a hernia had been bserved. In ad dition, both the outpatient and inpatient records were checked to make sure that hernia other than those described had not developed before the completion f the study

Results

Seventeen of the 82 infants had exter nal hernias, an over-all incidence of 20 %. As shown in Table 1 the frequency of inguinal hernia in infants weighing less than 1500 g greatly exceeded that in infants weighing more than 1500 g Five of the seven infants in Group I had inguinal hernia only (in one instance inguinal hernias were bilateral) and in two both inguinal and umbilical hernias were present

TABLE 1

Group	Total no. of cases	No. with hernia	Number of infants: Inguinal only	Umbilical only	Inguinal and umbilical
I	*8	7 (25 %)	6	0	
II	34	10 (16.5 %)	3	6	1

None of the infants in Group I had only umbilical hernias. Umbilical hernia alone on the other hand, occurred in six of the 10 infants in Group II and this type of hernia was twice as common as inguinal hernia

All of the inguinal hernias were detected before the age of 6 months none became incarcerated and all have been repaired without incident and one of the umbilical hernias as well

Discussion

Hernias may be defined as the protrusion of a viscus or its coverings through the walls of the cavity normally enclosing it The great majority of hernias are abdominal, and can be classified as external or internal External hernia extend to the surface of the body and result from congenital weakness of the abdominal musculature and fascia and/or increased intraabdominal pressure On the other hand internal hernias are protrusions within the body cavities.

In infancy and childhood, the most frequently seen hernias are of the external type namely inguinal and umbilical. Inguinal hernias may be grouped int direct or indirect types. These hernias are far commoner in the male (93%) and are most ften right sided (R:L ~ 1) In the indirect type herniation occurs along the spermatic cord, and follows the inguinal canal into the scrotum, while in the direct type it occurs through Hesselbach s triangle and protrudes into the scrotum. In infancy inguinal hernias are almost always indirect (3). Normally the testis reaches the scrotal sac by the end of the eighth month f fetal life The upper portion of the processu vaginalis obliterates at or shortly after birth. If this fails to occur a congenital indirect inguinal hernia usually results. If the e t re processu vagi-

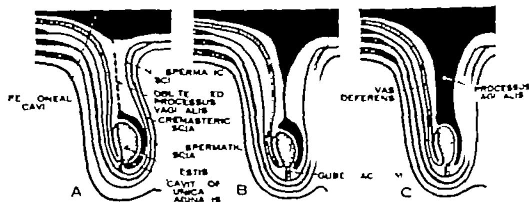


Fig. 1 A Normal obliteration of the processus aginalis. B incomplet obliteration of the processus vaginalis resulting in congenital indirect inguinal hernia. C patent processus vaginalis with extension of the hernia int the scrotum.

nalis remains open, the hernia extends to the lower pole f the testis, resulting in a scrotal hernia (Fig 1)

In the female the processus vaginalis undergoes a similar development during embryonic life. In this case the hernial sac is contiguous with the round ligament of the uterus. These hernias almost never disappear spontaneously often produce symptoms and may become incarcerated. In Pott series of 35 infants less than 4 months old, 26% were, or had been, incarcerated. On the other hand, in children over 18 months old, only 6% had become incarcerated [7]. As trusses frequently prove unsatisfactory and surgery is well withstood in early infancy most advocat early surgical repair

Umbilical hernias generally consist f a peritoneal sac covered by fat and skin. A firm rim of connective tissue representing fused anterior and posterior rectus and transversalis fascia encircles the hernia. In infancy these hernias tend t be small (1 2 cm in diameter) and almost never become incarcerated. These are commoner in the female (particularly Negroes) due perhaps, to their less well-developed musculature. Woods found that 93% of these hernias disappeared without strapping. In her opinion, any locally applied restrictive appliance may actually hamper spontaneous disappearance by interfering with maturation f abdominal musculature

Dunham considers prematures especially prone to umbilical hernia but does not state the incidence She quotes Ylppö s classical paper in which he found that premature infants were more frequently subject to both inguinal and umbilical hernia than the full term and the lower the birth weight the higher the incidence However Rambar & Goldberg, studying 830 premature infants, found no corresponding increase in the lighter weight groups of inguinal hernia and an over-all incidence of 4.8% in prematures over 1000 g As Keith had noted an incidence of 4 4% in 1000 full term infants in the first year of life no significant difference appeared to be present [5]. By the age of 5 months, almost all of Rambar & Goldberg s cases had been detected. As many cases in the present study have been followed for more than one year it seems probable that the incidence reported is fairly accurate

In this study the incidence of umbilical hernia is significantly less than that found by Hess in prematures, and is the same as that found by Woods in full terms (20%) This may be due to chance selection of infants, different criteria, or only moderately good follow up of some of the infants. On the other hand, the incidence of inguinal hernia found here is much greater than that found by others in full term infants (1–4%) [5 6] and is particularly high in infants of low birth weight This also appeared to be the case in Knox s study As inguinal hernias in infants result not from muscular weakness but from incomplete obliteration of the processus vaginalis, this is a not unexpected finding

None of the hernias became incarcerated and all were repaired early However this series is too small to warrant any conclusion regarding the value of elective repair of inguinal hernia in early infancy in the prevention of incarceration,

Admittedly the numbers are small. However the high incidence of hernia in these premature infants seems significant The figures suggest that the lower the birth weight the higher the incidence of inguinal hernia On the other hand, the

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This figure is reproduced from Hamilton, W J Boyd, J D & Mossman, H W *Human Embryology* Heffer Cambridge, 1945, with the permission of the publishers.

higher the birth weight, the lower the incidence and the more frequent is umbilical hernia.

Summary

Data on the incidence of external hernia during the first year of life in 82 healthy premature infants is presented. Twenty per cent of the infants had either inguinal or umbilical hernia or both. Infants weighing less than 1500 g at birth were found to have a higher incidence of inguinal hernia. This is attributed to incomplete obliteration of the processus vaginalis as a result of premature birth. Infants weighing more than 1500 g at birth had a higher incidence of umbilical hernia. The incidence of inguinal hernia appears to be significantly increased in premature infants. Contrary to other reports, the incidence of umbilical hernia in this series of premature infants does not appear to be greater than that reported in full term infants.

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Present address
Pediatric Clinic
Karolinska Sjukhuset
Stockholm 60
Sweden

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From the Department of Pediatrics, Rigshospitalet Copenhagen, and the Department of Biochemistry and Nutrition, Polytechnic Institute Copenhagen

Effect of Synkavit[1] and Vikastab[2] on Bilirubin and Plasma Prothrombin

by HOLGER V DYGGVE, EBBE SONDERGAARD and HENRIK DAM

Several authors [1 4 6 7 11 14], have studied the effect of certain vitamin K compounds with regard to the production of hemolytic anemia and kernicterus in premature infants. The general finding is that intramuscular administration of relatively large amounts of simple vitamin K substitutes, e.g Synkavit or disodium menadiol bisulfite causes an increase in serum bilirubin, whereas injection of vitamin K_1 does not

The effect is believed to be associated with oxidation of hemoglobin to methemoglobin by menadione [5] and with a limited ability to conjugate bilirubin with glucuronic acid [16] a characteristic of the premature infant

Related studies with vitamin E-deficient rats [2] have shown that Synkavit and disodium menadiol bisulfite (10 mg i.m. per 100 g body weight) produced hemoglobinuria whereas vitamin K_1 emulsion (7–40 mg i.m. per 100 g body weight) and Vikastab (10 mg i.m. per 100 g body weight) had no such effect.

Corner *et al* [6] determined the serum bilirubin level in premature infants given Vikastab intramuscularly in doses varying from 5 to 60 mg and found it essentially the same as in untreated premature babies. Prothrombin levels were not indicated.

We (E.S., H.D) have compared, in vitamin K-deficient chicks the effect on prothrombin time of equimolecular high doses of various vitamin K-active compounds at various intervals from the time of intravenous injection, using the technique described earlier [8 9]. We found that disodium menadiol bisulfate acted much more slowly than Synkavit, menadione or disodium menadiol bisulfite Vitamin K_1 acted faster (in chicks) than any of the other compounds. The results are shown in Fig 1

In newborn infants with prolonged prothrombin time, we (H.V D) compared the effect of a single intramuscular dose of 10 mg of Synkavit (stoichiometrically equivalent to 3.53 mg of menadione) with that of Vikastab (corresponding to 10 mg of menadione) at various times after the injection. The technique was as described by Dyggve *et al* [12] The results are presented in Figs. 2 and 3

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[1] Tetrasodium 2 methyl-naphthalene-1 4-diol diphosphate (tetrasodium menadiol biphosphate).

[2] Potassium menaphthosulfate (dipotassium menadiol bisulfate)

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(H. D) Department of Biochemistry and Nutrition
Polytechnic Institute
Copenhagen K.
Denmark

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Department of Pediatrics, University of Gothenburg Gothenburg Sweden

Studies on Leucin Induced Hypoglycemia

by JOHAN GENTZ, ORLA LEHMANN and ROLF ZETTERSTRÖM

The syndrome of leucin-induced hypoglycemia was described in 1956 by Cochrane, Payne Simpkiss & Wolf [7] Leucin and isovaleric acid were found to cause a marked fall in the fasting true blood sugar level in three members of a family with so-called spontaneous idiopathic hypoglycemia A similar effect of leucin was noted in another child with hypoglycemia due to islet cell hyperplasia. Other studies on hypoglycemia precipitated by leucin have subsequently been reported [6 10 11 12]. Mostly the findings of Cochrane *et al* have been confirmed, the only matter of controversy being whether isovaleric acid really has any hypoglycemic action in patients with this particular syndrome Thus Grumbach *et al* and Mabry *et al* were unable to induce hypoglycemia by the administration of isovaleric acid. On the other hand, they demonstrated that lpha-ketoisocaproic acid may have an hypoglycemic action. Mabry *et al* stated that isoleucin may also lower the blood sugar level.

Since ingestion of leucin in those individuals sensitive to this amino acid causes the same rapid drop in the blood gl cose level as does insulin when given by the intravenous route to healthy subjects, Cochrane *et al* suggested that leucin may enhance the effect of circulating insulin or may increase the release of this hormone from the islet tissue In fact the finding of Yalow & Berson that the administration of leucin increases the plasma insulin concentration as measured by immunoassay in 4 out of 6 subjects with leucin-sensitive hypoglycemia favours the assumption that insulin secretion i augmented. In this connection the observation that leucin has been found to have a marked hypoglycemi effect in patients with islet cell tumours [15] may also have some relevance

In this communication the studies on two children with the leucin-sensitive type of hypoglycemia are reported and the results obtained are discussed with regard to the current concept that the hypoglycemic state prod ced by leucin may result from its action on the mechanism of insulin secretion.

Case Histories

Case 1

L. J female infant admitted to the Children Hospital Gothenburg, t an age of 5 months because of convulsions.

She is the second child of a mother with a traumatic epilepsy There was no fall of the mother blood sugar on high protein feeding Pregnancy was normal; delivery was by cesarean section 3 weeks after term Birth weight 3000 g head circumference 34 cm.



Fig 1. Case 1 t an age of 18 months. She has con ergent strabismus.

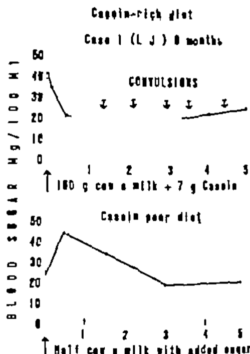


Fig — Case 1 The effects of casein-rich and casein-poor diets on the blood sugar The prompt effect of protein loading is quite evident

The infant was fed whole cow s milk formula with added saccharose She developed normally until the age of 3 months when repeated generalized convulsions appeared.

Physical examination on admission revealed a rather plump infant with a weight of 6 0 kg She w not definitely mentally subnormal. Strabismus wa the only abnormal finding (Fig. 1)

She had several fit daily during the first week in the hospital These generally appeared around 1 p.m., when she had not been fed for 4 hours. Before the convulsions she turned pale and perspired profusely The true blood suga level was then found to vary between 30–60 mg per 100 ml.

EEG examination did not reveal any abnormalities, even if the blood sugar level was as low as 40 mg per 100 ml.

Special i restigations When given a high casein, low carbohydrat test meal there was a rapid fall of the blood sugar level (Fig *) She flushed, sweated and had f ve fits during the following four hours but did not lose consciousness. When a casein poor meal with extra sugar was given, she had an initial increase of the blood sugar which then returned to the initial low level (Fig 2). However she d d not exhibit any real symptoms of l ypoglycemia.

Course nd treatment. When a diagnosis of leucin-sensit ve type of hypoglycemia had been made she was put on a low protein, high carbohydrat diet and was fed every third hour Under that regimen there was marked mprovement She became more li ely and had only one or two f t week. By 1 months of age the convulsions had l most completely subsided. She was however slightly mentally subnormal.

At an age of 16 months he relapsed ith repeated con ulsions and a rapid deteriora-

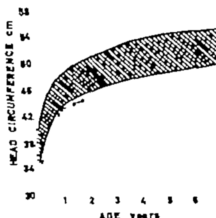


Fig. 3. Case 1. Serial determinations of the head circumference. The shaded area gives the growth of the skull with 99.5 % confidence in normal girls as reported by Westropp & Barber. The child is slightly microcephalic.

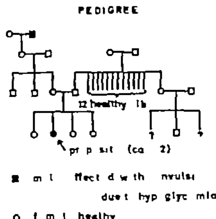


Fig. 4. Pedigree for Case —

tion of the mental state because the dietary prescriptions were not followed. She became immobile and lost the capacity to stand. When 18 months old she was readmitted. With proper diet she improved quickly and within another month she was able to walk.

At an age of 20 months she was slightly microcephalic with a head circumference of 44 cm (Fig. 3). Pneumoencephalography revealed slight but definit brain atrophy. EEG records were still within the normal range.

Case 2

U. B. J., girl, was admitted to the Children Hospital, Gothenburg at an age of 4 years because of hypoglycemia.

She is the product of the second pregnancy of a healthy mother. The great-grandfather (for pedigree cf. Fig. 4) had fits due to hypoglycemia since childhood, the frequency declining with advancing age.

Pregnancy and delivery were uneventful. The child was born at term, birth weight 4000 g. She developed normally until the age of 4 months, when she had repeated attacks of generalized convulsions, usually in the early morning. The seizures gradually increased in frequency and at years there were 4–5 attacks every day. She became severely mentally retarded and was unable to stand or walk at 3 years. Although repeated EEG examinations had not revealed any abnormalities, a preliminary diagnosis of epilepsy was made and she was put on antiepileptic treatment, which was, however, quit ineffective. At age 3 years hypoglycemia was diagnosed and she was referred to this hospital for further treatment.

Physical examination on admission revealed a severely retarded brain-injured child. She had a tottering atactic gait but was not really spastic. She was able to speak a few words but no sentences. The intellectual development corresponded to an age of 12–24 months, the variation depending upon what functions were tested.

In the hospital she had several hypoglycemic attacks with fits. Pronounced prodromes characterized by drowsiness, irritability, sweating and flushing were present. During the attacks the true blood glucose level was below 30 mg per 100 ml.

Special examinations. The sensitivity to

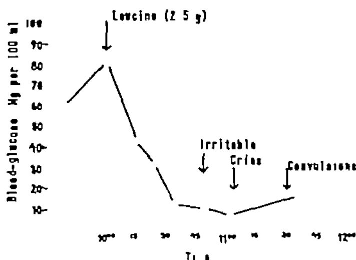


Fig 5. Case 2. The effect of L-leucin on the blood sugar A marked hypoglycemia appeared within 30 minutes after the administration of the amino acid.

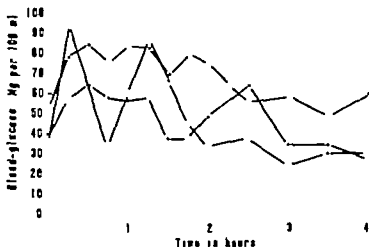


Fig 6. Case 1 The result of three different oral glucose tolerance tests performed at age of 9 months. An instability in the regulation of the blood sugar is obvious.

intravenously administered insulin was increased. When 0 15 g L-leucin per kg body weight was taken by mouth there was a drop in the blood glucose level from 83 to values below 20 mg per 100 ml within half an hour (Fig 5) She became irritable, followed by unconsciousness and generalized convulsions. The symptoms disappeared following the intravenous administration of glucose Tests for adrenocortical and thyroid function were normal.

EEG revealed grossly normal findings. Pneumoencephalography demonstrated brain atrophy

Treatment and course When the child was put on a low protein, high carbohydrate diet and the number of meals was increased, there was a marked improvement of her general state, she became much more alert and the fits disappeared promptly When seen one year after treatment had been started her mental st t had improved although she revealed symptoms attributable t permanent brain damage.

Special Studies on Carbohydrate Metabolism

Material and Methods

For the leucin tests L-leucin containing some isoleucin (British Drug Houses Ltd., laboratory reagent) was used. Two different preparations of isovaleric acid suspended in water were given, isovaleric acid purum (Kebo 84560) with a purity of 97–98% and isomer free isovaleric acid purіss. (Kebo 86002), purity 99.99%. Beta-hydroxy-isovaleric acid and senecioic acid were kindly supplied by Dr L I Woolf (Medical Research Council, Population Genetics Research Unit, Oxford) For the method of preparation, cf Woolf [17]

"True" blood glucose was estimated according to Ek & Hultman [8]. The urinary excretion of adrenaline and noradrenaline was determined by the use of a fluorim ric method (Carlsson, Rasmusson & h stjarneen). Our thanks are due to Mr Waldek, Department of Pharmacology University of Gothenburg for these estimations

Results

Most of the tests to be reported were performed in Case 1 essentially the same results were also obtained in Case *

Oral glucose tolerance tests The response to oral loads of 1.5 g glucose per kg body weight was essentially normal although an instability of the blood sugar regulation is obvious (Fig 6)

Blood glucose during insulin tolerance tests The intravenous administration of insulin in a dose of 0 1 unit per kg body weight caused an immediate and marked drop of the blood glucose level the return to the original level was delayed as is demonstrated in Fig 7 A slight but significant elevation of pulse rate and blood pressure was noted during the insulin-induced hypoglycemia Otherwise there were no real hypoglycemic symptoms. In Case 2 the sensitivity to insulin wa more pronounced.

Test with leucin, isovaleric acid beta hydroxyisovaleric acid and senecioic acid In all experiments the child was given a regular meal 4 hours prior to the administration of the substance to be tested In order to get information about the blood sugar regulation under basal conditions the blood sugar was estimated three or more times before the tart of the experiment. The te substance w given by rapid inf sion through a naso-gastric catheter

L ucin 0.3 g per kg body weight wa g en several times to Case 1 in order to confirm that the sensitivity to thi mino acid persisted The results of some of the xperiments are hown in Fig 8 Curve 3 shows the prompt hypoglycemic effect of leu in lthough the hild did not develop any real hypoglycemic ymptom d ring

INSULIN TEST

L J 18 months

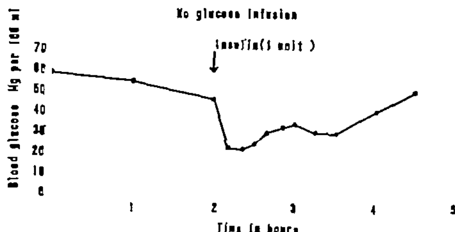


Fig 7 Case 1 Intravenous insulin tolerance test. The return to the original blood sugar level is delayed indicating an increased sensitivity to insulin.

LEUCINE TESTS

(L J)

x—x 100 ml of 5 0 % glucose solution per hour by nasal
(Age 8 months) drip 0 5 g leucine (0 07 g per kg body weight) was
infused during 1 2 min s

— No glucose infusion 3 g leucine (0 3 g per kg body
(Age 18 months) weight) was given during 1 2 min s

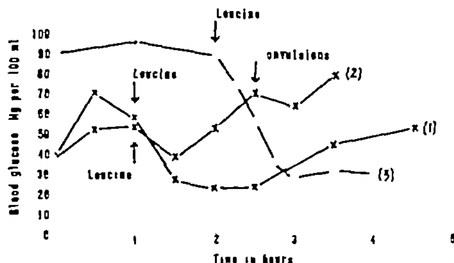


Fig. 8. Case 1 Effect of leucin on the blood sugar in three different experiments. In two of them leucin was given during continuous administration of glucose I one of the experiment the girls developed fits despit blood sugar level within he normal range

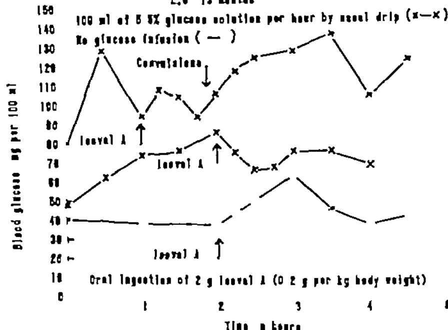


Fig. 9 Case 1 Effect of isovaleric acid on the blood sugar level in three different experiments. No significant changes were observed. In one of the experiments fits appeared, although the blood sugar level remained normal.

this experiment. Curves 1 and 2 represent the changes of the blood sugar level in experiments when there was a continuous intragastric infusion of glucose solution (0 6 g per kg body weight) in addition to the one dose administration of leucin. In one experiment (Curve 1) there was a drop in the blood sugar following the administration of leucin, but the child remained symptom-free In another (Curve 2) the effect of leucin on the blood sugar was insignificant but convulsions appeared after 90 minutes, although the blood sugar at that time was 0 mg per 100 ml.

The results demonstrate that the continuous administration of glucose does not always prevent a reduction of the blood sugar level in those sensitive to leucin. It is also evident that fits may appear following the ingestion of leucin, even if the blood glucose concentration remains within the normal range

Effect of isovaleric acid In three experiments isovaleric acid in a dose of 0.2 g per kg body weight was given, in two of them glucose was given continuously The blood sugar level increased in the experiment when no glucose was given (lower curve), and decreased in another when there was a continuous infusion of

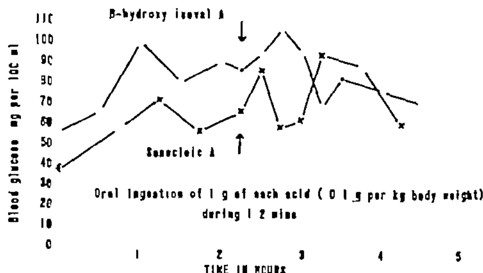


Fig 10 Case 1 Effects of beta hydroxyisovaleric acid and senecioic acid on the blood sugar level. There were no significant changes.

glucose (Fig 9) The purest preparation had been used when the blood sugar increased In a third test with glucose the blood sugar level remained on a high level during the whole period of observation although it was very unstable In this experiment tonic and generalized clonic convulsions lasting for about 4 minutes appeared 50 minutes after the administration of isovaleric acid although the blood sugar level was 100 mg per 100 ml. The significance of thi finding is difficult to evaluate

Effects of beta-hydroxyisovaleric acid and senecioic acid As is seen from Fig 10 the administration of these two substances did not exhibit any significant effect on the blood sugar level which is in accordance with the findings of Woolf No convulsions or other symptoms appeared In both experiments glucose was given continuously

Urinary output of adrenaline and nor adrenaline in connection with various tests In insulin induced hypoglycemia the urinary excretion of adrenaline is known to increase five to twenty times [9] Since leucin causes about the same reaction on the blood sugar level in those sensitive to this amino acid as does insulin in healthy subjects, the effect of leucin ha been compared with that of insulin on the urinary output of catecholamines The effect of those degradation product of leucin tested in the present studies ha also been investigated For experimental conditions, cf Broberger Jungner & Zetterström [*]

A is seen from Table 1 there wa a

TABLE 1 *Urinary excretion of adrenaline and noradrenaline during various tests*

L. J., 13 months Following the administration of leucin there was a significant increase of the urinary output of adrenaline although not t the same extent as following intravenously given insulin. The three other substances tested did not cause any changes. The values are gi ven in micrograms per hour

Test	Before	After
Leucine (Fig. 8)		
Adrenaline	0.5	1.1
Noradrenaline	0.6	0.3
Isovaleric acid (Fig. 9)		
Adrenaline	0.8	0.6
Noradrenaline	1.3	1._
β-hydroxy-isovaleric acid (Fig 10)		
Adrenaline	2.4	1.8
Noradrenaline	2.7	_0
Senecioic acid (Fig 10)		
Adrenaline	0.7	0.3
Noradrenaline	2.3	_5
Insulin (Fig. 7)		
Adrenaline	0.5	2.0
Noradrenaline	0.6	1.0

significant increase of the adrenaline out put following the administration of leucin, although not to the same extent as when insulin was injected intravenously When isovaleric acid beta hydroxyisovaleric acid or senecioic acid were given there was no response. It may be ssumed that the increase of the adrenaline output in the urine following leucin administration is a consequence of hypoglycemia

Discussion

Much remains to be elucidated before the pathogenesis f leucin-induced hypoglycemia can be fully explained. Strong evidence is in favour f the opinion that there is in leucin-sensitive hypoglycemia an increased output of insulin from the pancreas although the way in which leucin acts in that respect is completely obscure Two possibilities may be discussed. One explanation is that leucin catabolism is abnormal and that leucin or some leucin metabolite may change cellular metabolism in such a way that insulin output will in crease as a secondary consequence The other explanation is that leucin or some of its degradation products acts directly on the islet tissue of the pancreas

From experiments reported by Butter field, Whichelow Wright & Woolf [4] it seems quite clear that leucin has no direct action on the uptake of glucose in peripheral tissues in those sensitive to this amino acid, the effects instead solely being due to a transient rise in the plasma insulin activity

However the observation that convul sions may appear following leucin ingestion despite a blood sugar level maintained within the normal range by continuous glucose administration may indicate that the syndrome of leucin sensitivity is more complicated than simply a primarily in duced hypoglycemia with its consequences.

The rapidity by which permanent and severe brain damage may develop in the syndrome of leucin-induced hypoglycemia is another factor which might point to a more profound metabolic derangement than simple hypoglycemic episodes. Case 1 was slightly microcephalic and in Case * there was a high degree of brain atrophy One of the patients reported by Mabry *et al* was also severely brain damaged with head circumference f only 39 cm at an age of 19 months. Although encephalopathy is considered to be a common com plication in repeated attacks of hypoglycemia in infancy [13] pronounced

LEUCINE
$(CH_3)_2CH-CH_2-CH(NH_2)-COOH$

α KETOISOCAPROIC ACID
$(CH_3)_2CH-CH_2-CO-COOH$

ISOVALERIC ACID
$(CH_3)_2CH\ CH_2\ COOH$

ISOVALERYL CoA
$(CH_3)_2CH\ CH_2-CO-SCoA$

β METHYLCROTONYL CoA
$(CH_3)(CH)>C\ CH-CO-SCoA$

β HYDROXYISOVALERYL-CoA
$(CH_3)(CH)>C(OH)-CH-CO-SCoA$

β METHYLGLUTACONYL CoA
$HOOC-CH-C=CH\ CO-SCoA$ (CH_3)

β-HYDROXY β METHYLGLUTARYL CoA
$HOOC\ CH_2\ C(CH_3)(OH)-CH_2-CO-SCoA$

ACETOACETATE

ACETYL CoA

MEVALONIC ACID HSCoA
$HOOC\ CH\ C(CH)(OH)\ CH\ CH_2OH$

CHOLESTEROL

Fig 11 Intermediates in leucin metabolism.

atrophy of the brain does not seem to be as common in other types as that precipitated by leucin [3]

It may be considered that there is in the syndrome of leucin sensitivity some block in leucin metabolism causing the accumulation of some of the coenzyme A intermediates formed in leucin metabolism [1] (Fig 11) thus transiently binding CoA necessary for other metabolic processes. Such an assumption presupposes however that isovaleric acid causes the same changes as does leucin. Originally Cochrane *et al* found that isovaleric acid lowered the blood sugar but this finding has not been confirmed either by Grumbach *et al* or Mabry *et al* or in our studies. It thus seems as if only leucin or alpha ketoisocaproic acid or both are active It should, however be pointed out that one of our patients developed fits following the oral administration of isovalerate even though there was no effect on the blood sugar level. Further studies are needed before this problem can be considered a completely solved That beta hydroxyisovaleric acid and senecioic acid are ineffective is explained by the fact that these

substances do not enter the pathway of leucin metabolism.

Most probably the disorder is inherited as an incomplete dominant (the family described by Cochrane *et al.* and our Case *). That the disorder is genetically determined is in accordance with the concept that the syndrome develops due to some inborn error of metabolism.

Summary

Two typical nonrelated cases of leucin-precipitated hypoglycemia are described. Both patients showed evidence of severe atrophy of the brain. Since leucin was found to induce fits even if a fall in the blood sugar was prevented by the continuous administration of glucose, the symptoms *in the syndrome of leucin-induced hypoglycemia may not solely develop as the result of an abnormally low blood sugar level.*

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Barnsjukhuset
Göteborg
Sweden

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From the Research Department of Ulleråker Hospital, University of Uppsala, and the Pediatric Department and Institute of Histology University of Göteborg Sweden

Chromosome Studies in Eleven Families with Mongolism in *More than One Member*

by HANS FORSSMAN and ORLA LEHMANN

Previous Research

Ever since Lejeune *et al* (1959) described 9 cases of mongolism with 47 chromosomes, which led to an extensive series of publications by a large number of authors, it has been known that the anomaly is mostly characterized by trisomy for chromosome number 21 In 1960 it was also learned that other kinds of chromosomal aberration occasionally occur in this disorder Studies of families with many instances of mongolism [2–11] and of children with this anomaly born to unusually young women [1_] revealed an abnormal karyotype assumed to be caused by translocation between a number 21 and 15 chromosome (Denver nomenclature) generally designated as 15/21 translocation The children in whom this was observed had 46 chromosomes The translocation was transmitted by clinically normal women with 45 chromosomes. Forssman & Lehmann [5] discovered the same translocation in a normal boy (His family belongs to one of the 11 described in this paper) A third deviation in this anomaly interpreted as a 21/21 or 21/22 translocation was described by Penrose *et al* [11] and Fraccaro *et al* [6]. Both these groups of authors discovered the deviation by chance in cases in which mongolism was not of familial occurrence *and in which the mothers were not particularly young*

Obviously trisomy for the 21st chromosome is by far the most common chromosomal aberration occurring in mongolism. The best way to get an idea of how often the more infrequent aberrations occur would be to study the karyotype in a non selected series of newborn children with mongolism It may be assumed that several authors have already begun series of this kind but it will naturally be some time before they will get enough data for statistical analysis.

Present Investigation

Material

We went through about 1400 cases of mongolism, most of them in institutions, for the ones who had at least one relative with the same disorder The majority of them, or 1 6[illegible] were reported by one of us (Forssman [4]) in connection with a study made between 1953 and 1959 of the inmates of *Swedish institutions for the feeble minded.*

Starting with these 1400 probands, we found 14 families with more than one member suffering from mongolism. In several f these cases the familial occurrence was discovered more or less by chance as the amount we were able t study each family varied greatly and depended for one thing upon how old the proband was. As much informa tion as possible was collected from the staff at the institutions, physicians and others.

For various reasons we had to restrict the present investigation t only 11 of the 14 families. Table 1 gives some f the essential data bout these families.

Method

W studied the chromosomes of leucocytes from circulating blood, using a slight modification of the technique described by Hungerford *et al.* [7]. As rule at least 25 mitoses were counted and, if the same number of chromosomes were found in more than 20 of these mitoses, it was accepted as the definite hromosome number Idiograms of three t eight mitoses were then made. We also made long term cultures of fibroblasts from skin according t the technique described by Bergman [1] but unfortunately we were not able t do so in all the cases. Thus we are not ble t exclude the possibility of mosaicism in most of the cases, but in no case did the cultures point to this eventuality

Results

In families 1-6 mongolism occurred in two siblings. In family 7 it occurred in the paternal aunt of a child with this anomaly and in family 8 in two cousins whose mothers were sisters. In these 8 families, the trisomy for the 1st chromosome usual in this anomaly wa noted.

The mother of 8*a* refused to let us take a specimen from her child. Thi child s cousin the boy 8*b* died shortly after he was born, but we were kindly informed of his karyotype by the University of Lund.

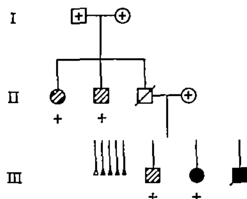
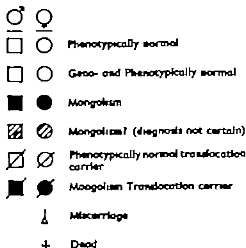


Fig 1. The pedigree of family 9 in Table 1 (Key t symbols in pedigrees.)



We ourselves determined the karyotype of the two mothers who were sisters. They both had a normal idiogram.

In families 9 to 11 mongolism was hereditary in the true sense, the chromosomal translocation occurring in several generations These families merit a short description

Family 9

Family 9 is seen in Fig 1 The husband and wif in generation I were said to have



Fig. _ The girl III 7 from family 9.

been intelligent enterprising and constitutionally normal they had been dead some time but we met several people who knew them

II 1 1876–1887 Mentally deficient never went to school.

II 2 1870–1884 Mentally deficient never talked properly According to a schoolteacher who had lived on the same farm as the family since 1910 when I 2's two grandchildren who definitely had mongolism were born I _ had said that they were the same kind of children a my dead babies While it is not entirely certain that II 1 and II 2 had mongolism we felt we must give them the symbol for suspected cases.

II 3 1882– highly gifted normally built well preserved 70-year-old examined by us.

II.4 1887–1953 said to be intelligent and normal physically

Generation III II 4 had five spontaneous abortions before she got a living child.

III 6 1919 died 8 days after birth. The cause of death is not known, the symbol for suspected mongolism is based on relatively vague testimony

III 7 1921–1923 Photographs, including the one in Fig 9 show that this child definitely suffered from the anomaly

III 8 1944– typical case of mongolism, with great mental deficiency examined by us. He could walk, but could not speak at all.

Cytologic observations

II 3 It was only possible to culture the blood of this man Many mitoses were obtained and 45 chromosomes occurred in over 75 % of them Only three small acrocentric chromosomes were noted in all the mitoses studied Three mitoses were used for determining the karyotype All of them showed two small acrocentric chromosomes lacking Instead there was a small unpaired chromosome resembling the ones in pairs 19 and 20 It seemed a little larger than these however and may have been a translocation chromosome of type 1/21 or 1/22

III 8 Cultures were made of both the blood and skin. Many mitoses were seen in blood cultures, and in over 80 of the counted mitoses there were 46 chromosomes containing four small acrocentric chromosomes. Four idiograms were made revealing the same karyotype a the father s except for one small acrocentric chromosome more than the father had. Thi chromosome could be fitted into pair 21 increasing the genetic material

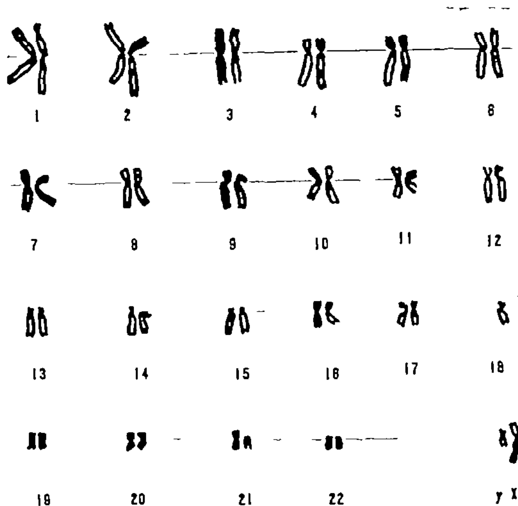


Fig. 2. Idiogram of the boy III: 8 from family 9. Translocation of type 21/21 or 21/22, here taken as 21/21

there to 3 chromosomes (Fig. 3). The same results were obtained in skin cultures. Three karyotypes were determined in mitoses from two transplants.

Family 10

Family 10 is shown in Fig. 4. Lehmann & Forssman [8] described this family in detail in this journal.

Cytologic observations

II 1. Cultures of the blood showed that the father had 46 chromosomes and a normal idiogram.

II [illegible]. Cultures of the blood showed that the mother had 45 chromosomes in over [illegible]0 out of [illegible]5 counts. Three determinations of the karyotype gave the same results. There was monosomy for chromosome

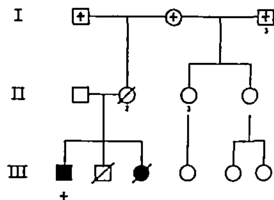


Fig. 4. The pedigree of family 10 in Table I.

1 2 3 4 5 6

7 8 9 10 11 12

13 14 15 16 17 18

19 20 21 22 X X

Fig. 5. Idiogram of the girl III 3 from family 10. Translocation of type 15/21

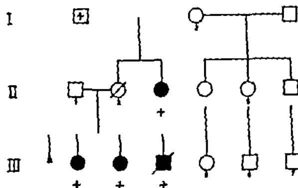


Fig. 6. The pedigree of family 11 in Table I

number 21 or 22 and for one of the chromosomes 13 to 15. Instead there was an extra chromosome resembling the ones in group 7–12, probably translocated from the places for monosomy.

III.2. Blood cultures of this phenotypically normal boy showed 45 chromosomes in more than 20 out of 25 counts. Eight good mitoses were used for determining the karyotype. The same type of transloca tion was observed as in the boy's mother.

III 3. Blood cultures of this girl with mongolism showed 46 chromosomes in more than 20 out of 23 counts. She had a small acrocentric chromosome more than her mother and carried the presumed 15/21 translocation. Four mitoses were carefully examined (Fig. 5).

Family 11

Family 11 is seen in Fig. 6.

I. – The chromosomes of the proband's maternal grandmother were studied on two occasions and both times a normal idiogram was found.

II 1. Two blood cultures were a failure. In view of the observations in the wife (II) and the occurrence of mongolism on the mother's side no more attempts were made to determine the karyotype.

II. – The blood of the proband's mother was cultured on two different occasions and the results were the same both times. There were 45 chromosomes and the karyotype in eight good mitoses showed the 15/21 type of translocation.

III.4. Skin cultures in this case were published by Ek *et al* [3]. The patient had died before we began our investigation, and before we knew of these authors results. The boy—according to Ek and co-workers—had 46 chromosomes and carried the 15/21 type of translocation like his mother.

Thus in 8 of our 11 families with more than one instance of mongolism there was the usual trisomy for the 21st chromosome and in the other 3 families there were translocations of two different types.

When grouping this way, however, it must be remembered that Moorhead *et al* [10] observed a child with mongolism who showed 21 trisomy though its mother carried the 15/21 type of translocation.

TABLE 1 *Certain essential data in the eleven families*

Case	No	Sex	Diagnosis based on	Relationship	Maternal age in years	Idiogram	Other siblings
1		M	Authors exam.	Siblings	31	Trisomy	dead perinatally (one a t a
1	b	F	Authors exam.		35	Trisomy	
		F	Authors exam.	Siblings	33	Trisomy	5 said t be normal, all older
	b	M	Authors exam.		41	Trisomy	
3	a†	M	Hosp. records	Siblings	23	—	3 normal, exam. by authors
3	b	M	Authors exam.		24	Trisomy	
4	a	F	Authors exam.	Siblings	36	Trisomy	said t be normal, 1 dead at b
4	b†	M	Authors exam.		40	—	
5	a†	M	Hosp. records	Siblings	4	—	1 normal sister exam. by autho
5	b	F	Authors xam.		30	Trisomy	
6	†	F	Hosp. records	Siblings	40	—	Y siblings
6	b	F	Authors exam.		46	Trisomy	
7	a	M	Authors exam.	Sister's son	42	Trisomy	2 said t be normal
	b†	F	Hosp. records	P ternal aunt	45	—	4 said t be normal
8		F	Authors exam.	Cousins	34	—	1 normal brother exam. by aut
8	b†	M	Hosp. records		32	Trisomy	1 normal sisters, exam. by autho
9	†	F	Phot (Fig)	Siblings	34	—	See t xt
9	b	M	Authors exam.		37	Translocation	
10	a†	M	Hosp. records	Siblings	21	—	See text
10	b	F	Authors exam.		[illegible]	Translocation	
11	a†	F	Hosp. records		27	—	See text
11	b†	F	Hosp. records	Siblings	33	—	
11	c†	M	Hosp. records		25	Translocation	
11	d†	F	Inform. from family	Maternal aunt	30	—	

† = Dead before the start of this investigation.

We have previously suggested [5]—as have also Polani *et al* [12]—that the different kinds of translocation and the trisomy associated with mongolism might be of common origin a disorder in the nucleolar breakdown which makes the satellited acrocentric chromosomes apt to stick together The observations of Moorhead *et al* point to the possibility that some of our trisomic cases might have had a translocation-carrying mother or father

From Table 1 it may be calculated that the average maternal age was 34 0 years in the cases of trisomy and 30 8 years in the cases of mongolism with translocation. This difference points in the expected direction, i e to a higher maternal age in the trisomic cases than in the cases of tran location The difference is not statistically significant however which is not surprising in view of the small amount of material

Discu ion and Summary

Our investigation i based on selected material insofar a the very principle of selection contains a factor pointing to the possibility of heredity However a mon-

golism occurs in about 1 out of 600 babies, it should be possible for two siblings to get the same anomaly through pure coincidence As far as we can now tell this must have happened in the first eight of our families, where the only chromosomal abnormality we found was trisomy for the 21st chromosome

In the last three families, which showed two different forms of translocation, it should be right to speak of mongolism as a genetically transmitted defect.

In family 9 we observed genetic transmission of the syndrome through translocation of type 21/21 or 21/22 a type of translocation hitherto only described in two sporadic cases of the disorder Unlike the previously reported cases of inherited mongolism in family 9 it was a male who passed the translocation on to his children.

Family 10 s an example of the 15/21 type of translocation already observed in several familial cases and one sporadic case Here, too a phenotypically normal male carried the translocation, but he has not yet reached fertile age

Family 11 is also an example of the 15/21 type of translocation The woman I.2 had a normal karyotype and so either I 1 now dead, carried the translocation or else it was caused by chromosomal mutation during the oogenesis in I 2 The fact that I.2 also gave birth to a child with mongolism indicates that it was the man I 1 who carried the translocation. In none of the hitherto published studies had it been possible to track down the chromosomal mutation which led to the translocation.

None of the carriers of any of the types of translocation in our three families had a genotypically normal child. Thus three phenotypically normal translocation carriers produced 15 pregnancies, which resulted in six abortions, seven certain cases and one suspected case of mongolism and one phenotypically normal translocation-carrier

Acknowledgement

W are indebted t Dr S Bergman and Dr J Reitalu f the Bacteriologic and Genetic Departments f the University of Lund for information on the idiogram f the boy 8b in Table 1

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(H F) Research Dept.
Ulleråker Hospital
Uppsala
(O L.) Pediatric Dept. and Institut of Histology
Gothenburg
Sweden

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From Booth Hall Children's Hospital, Manchester England

Penicillin Versus Tetracycline in the Treatment of Childhood Osteomyelitis

by C. H. CULLEN and E. J HARGADON

Acute osteomyelitis in children is a common disease It is occasionally fatal, and despite modern therapy it may proceed to a chronic phase with severe destruction of bone the formation of sequestra and discharging sinuses. As many as 29% of acute cases may develop a chronic osteomyelitis [14].

Prior to the use of penicillin, the treatment of osteomyelitis was almost entirely surgical, but when penicillin was introduced the necessity for surgical intervention decreased considerably In recent years the combination of specific antibiotic therapy and surgical intervention has been stressed by Buchman [1], whilst Shandling [10] suggests that the local lesion should always be explored, and the bone decompressed by drilling Trueta [11] recommends antibiotic therapy and surgical intervention only if the local signs warrant it and usually after a period of observation of *4 to 48 hours.

Antibiotic therapy to be effective must be given in adequate doses, and must be used against a sensitive organism The organism usually responsible for acute osteomyelitis is a *Staphylococcus aureus* increasing numbers of which are resistant to penicillin. In ent osteomyelitis the incidence of penicillin resistance may vary from *0 % [10] to 100 % [*]

Gaisford [5] recommends that 1–* million units of penicillin should be given twice daily to children with acute osteomyelitis, changing the antibiotic after 48 hours if there is no response If the organism is resistant, this treatment has no effect, and serves only to delay effective therapy Other authors use a combination of penicillin with one of the tetracyclines [10 14] This combination of antibiotics is not synergistic, the effect being a simple summation of the individual effects [7] It is unlikely that an organism resistant to the tetracyclines and sensitive to penicillin will be responsible for osteomyelitis, and there does not appear to be much point in using this combination.

This paper is a study of the incidence of penicillin resistant organisms in the aetiology of acute haematogenous osteomyelitis in 58 children, and a comparison of the efficacy of penicillin therapy with the results obtained by a broad-spectrum antibiotic such as tetracycline

Patients studied

During the two years 1958 and 1959 6– children with osteomyelitis were treated t

TABLE 1 *Source of organisms recovered in 33 children with osteomyelitis*

Investigation	Nega tive	Posi tive
Blood culture	18	12*
Culture of pus from bone focus	3	*0*
Culture of pus from skin lesions	—	3
Culture of antral washings (maxillary osteomyelitis)	—	1
Culture of urine	—	1
	Total positive results	37*

Four patient had a positive result from both blood culture and from culture f pus from the bone focus.

TABLE * *Details of organisms recovered and their sensitivity to penicill n*

Penicillin resistant	*Staphylococcus aureus*	1?
	Salmonella dublin	1
Penicillin sensitive	*Staphylococcus aureus*	1?
	Streptococcus haemolyticus	1
	Total	33

this hospital Three patients who had a Brodie abscess and one patient with a local infection of the patella following burns were excluded from the survey The remaining 58 patients were available for study

Infecting Organism

Source of organisms (Table 1)

Organisms were recovered in 33 of these 58 patients. Blood culture was carried out in 30 patients and a positive result wa obtained in 1 In 23 patients pus obtained from the infected bone focus was submitted for culture A positive result was obtained in *0 cases, including four patients in whom the blood culture was positive In the other three patients the abscess had presumably been rendered sterile by treatment

The organism wa recovered from the urine in one patient from the nasal discharge and antral wa hings in a patient with osteomyelitis of the maxilla and from infected skin lesion in three patients.

Type of organism and sensitivity to antibiotics (Table 2)

Thirty-one of the 33 organism recovered were *Staphylococcus aureus* of which 17 were resistant to penicillin. There wa one infection by a penicillin resistant *Salmonella dublin* and one by a penicillin-sensitive haemolytic Streptococcus All the organisms were sensitive to the tetracycline group of antibiotics except the Salmonella, which wa sensitive to chlor amphenicol and streptomycin only

Eighteen of the 33 organisms recovered were resistant to penicillin and 15 were sensitive to it as shown by standard laboratory tests. It is noted that of the organisms recovered in this series, 54.5 proved resistant to penicillin

Antibiotic Therapy

In the re iew of the antibiotic therapy three cases were rejected because the initial treatment wa carried out lsewhere and i not definitely known

The remaining 55 patient were divided into two main groups accord ng to the initial antibiotic therapy Group 1 – 2. cases treated initially with penicillin. Group * *0 cases treated initially with a broad-spectrum antibioti

The 2. children in Group 1 re treated initially with penicill n either t home or

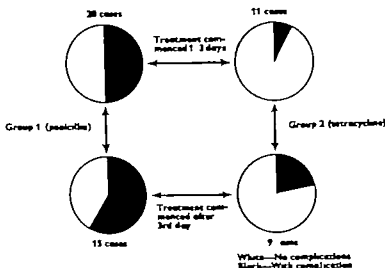


Fig 1 Diagram showing the incidence of complications in Group 1 and (White no complications; black, with complications.)

in hospital. The drug was changed within a few days if there was an inadequate clinical response or if the responsible organism when isolated, was found to be resistant to penicillin.

The 20 children in Group were treated from the beginning with a broad-spectrum antibiotic usually tetracycline The drug was changed on one occasion when a resistant organism was isolated and on two occasions because of nausea and vomiting

In both groups treatment was continued for period of three to four weeks.

These two groups have been compared relative to the incidence of complications, and to the length of stay in hospital

Incidence of complications Ideally children with osteomyelitis seen within the first two days of the onset of symptoms and treated with an antibiotic to which the infected organism is sensitive should recover without bscess formation or significant sequestration.

On this basis, complications are taken to include the formation of a soft tissue or bone abscess requiring surgical drainage sequestration requiring sequestrectomy or the development of a pathological fracture

Early treatment has been shown to be important in osteomyelitis [6] and therefore the cases in each group have been divided into (1) those who commenced treatment within three days of the onset of symptoms, and (2) those who commenced treatment fter this period. The incidence of complications is shown in Fig 1

Twenty of the 35 cases in Group 1 commenced treatment within three days of the onset of symptoms, and 15 after this period. Nineteen required drainage of an abscess Six of these later required sequestrectomy two of whom developed a pathological fracture

Eleven of the 20 cases in Group commenced treatment within three days of the onset of symptoms and nine after

TABLE 3. *Infections by penicillin resistant organisms treated initially with penicillin*

Name	Age yrs	Age mnths	Sex	Site	Source of organism	No. of days symptoms prior to treatment	Initial therapy	Progress and complications	No. of days stay in hospital
H. F.	14	11	M	Tibia	Pus	6	Penicillin ½ mega 6 hrly 21 days	Abscess drained 1st day No further complications	22
P. M.	2	0	M	Os calcis	Pus	2	Penicillin ½ mega 6 hrly 3 days Tetracycline 25 days	Abscess drained 3rd day No further complications	4
P. N.	5	7	M	Pubis	Pus	4	Penicillin ½ mega twice daily 3 days Tetracycline 8 days	Abscess drained 5th day No further complications	46
J. D.	8	5	M	Femur	Blood culture and pus	4	Penicillin ½ mega 4 hrly 3 days Tetracycline 20 days	Abscess drained 2nd day Sequestrectomy three times	395
K. Q.	6	1	F	Femur	Blood culture	3	Penicillin 1 mega 6 hrly 3 days Tetracycline 21 days	Abscess drained 2nd day Discharged in caliper	74
J. R.	6	4	F	Femur	Blood culture and pus	2	Penicillin 1 mega immediately ½ mega 6 hrly 2 days, ½ mega twice daily 3 days Tetracycline 21 days	Abscess drained 3rd day Recurrence in 3rd month settled with antibiotics	52
J. D.	11	7	M	Tibia	Pus (Salmonella)	2	Penicillin 600,000 units once a day for 3 days prior to admission Tetracycline 4 days Chloramphenicol 21 days	Abscess drained 2nd day No further complications	35
A. R.	12	9	F	Femur	Pus	3	Oral penicillin 4 days prior to admission, dosage not known. Tetracycline 25 days	Abscess drained 5th day Sequestrectomy twice	192
H. D.	7	10	F	Femur	Blood culture	3	Penicillin 1 mega immediately ½ mega 6 hrly 3 days. Tetracycline 23 days	Abscess drained 3rd day Sequestrectomy	85
J. K.	0	18/30	F	Maxilla	Antral pus	13	Penicillin ½ mega 6 hrly 7 days ½ mega twice daily 6 days, with Chlortetracycline 5 days	Antrum drained 5th day Discharged after 49 days. Re-admitted after one week and died	60
J. B.	0	2	M	Humerus	Pus	3	Penicillin days, dosage not known. Spiramycin 14 days. Erythromycin 14 days	Abscess drained 2nd day Sequestrectomy twice	70
A. H.		1	M	Humerus	Pus	4	Penicillin 1 mega 6 hrly 4 days Tetracycline 21 days	Abscess drained 4th day Sequestrectomy	83

1 mega = 1,000,000 units.

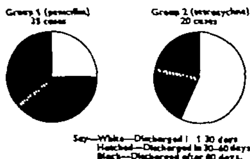


Fig 2. Diagram showing periods of length of stay in hospital. (White patients discharged within 30 days; hatched, patients discharged in 30–60 days black, patients discharged after 60 days.)

this period. Three children required drainage of an abscess, one of whom later required sequestrectomy and also developed a pathological fracture

The incidence of complications in Group 1 (treated initially with penicillin) was 54 % and in Group 2 (treated initially with a broad-spectrum antibiotic usually tetracycline) was 15 %.

Length of stay in hospital (Fig 2) The periods given for length of stay in hospital include readmissions for treatment of complications. The majority (74 %) of children in Group 1 required more than 30 days of hospital treatment. Nine children were discharged within 30 days of admission, 14 required between 30 and 60 days for their treatment and 12 were in hospital for more than two months.

Twelve children (60 %) in Group 2 were discharged within 30 days of admission four required treatment for between 30 and 60 days, and four were in hospital for more than two months.

Details of Treatment

There were 30 cases in which organisms were recovered and in which the antibiotic therapy was known. These are set out in Tables 3 4 and 5

Table 3 Twelve patients infected by penicillin-resistant organisms were treated initially with penicillin. This was given either prior to or following admission, and a change was made to a broad-spectrum antibiotic either for lack of clinical response or because the organism recovered was shown to be resistant to penicillin.

The one death in the series occurred in this group This was in an infant aged 18 days with maxillary osteomyelitis. The baby improved sufficiently to be allowed home, but was readmitted one week later and died with a cerebral abscess.

Also in this group is the solitary infection by a *Salmonella dublin* This occurred in a boy aged 1 years, who as an infant had been admitted to this hospital with gastroenteritis. As part of the treatment for this condition he was given an intra tibial drip, but developed an osteomyelitis at the transfusion site. The organism responsible for the original infection was a *Salmonella dublin*, which appeared to be identical with that recovered twelve years later He had no symptoms during the intervening period.

All 1 cases in this group developed complications, despite the fact that the majority commenced their treatment within three days of the onset of symptoms.

Table 4 This table shows four cases in which a penicillin-resistant organism was recovered, and which were treated from the beginning with a broad-spectrum antibiotic

Only one child in this group developed complications and he commenced treatment within 24 hours of the onset of

TABLE 4 *Infections by penicillin resistant organisms treated with broad-spectrum antibiotics*

Name	Age yrs	Age months	Sex	Site	Source of organisms	No. of days symptoms prior to treatment	Initial therapy	Progress and complications	No. days in hosp.
P B	1	6	M	Tibia	Nose and skin pustules		Tetracycline 21 days	No complications	21
P K.	2	3	M	Femur	Blood culture and pus	1	Chlortetracycline 1 day Tetracycline 6 days Erythromycin 8 days Chloramphenicol 14 days	Abscess drained 4th day Sequestrectomies at 1 & 16 months. Pathological fracture 19th month	19
P D	4	9	F	Femur	Blood culture	4	Tetracycline 1 day	No complications	23
P M.	3	5	M	Humerus	Blood culture	18	Tetracycline 20 day	No complications	23

symptoms. He was seriously ill on admission, and in pre-antibiotic days would almost certainly have died. He remained in hospital for more than two years, due in large part to unfavourable home conditions.

Table 5 This table presents 14 cases in which the infecting organism was found to be penicillin-sensitive Two children were treated entirely with tetracycline and recovered without complications, six were treated with penicillin alone and six children who commenced treatment with penicillin were changed to tetracycline owing to lack of clinical response Seven of these patients developed complications

These cases particularly those shown in Table 3 would appear to confirm that resistance of an organism to penicillin *in vitro* closely agrees with the clinical response of the infection to penicillin therapy

Discussion

Since the introduction of penicillin there has been a gradual increase in the proportion of cases of osteomyelitis due to an infection with a penicillin-resistant *Staphylococcus aureus*

Dennison [4] and Trueta & Morgan [1?] reporting large series of cases of osteomyelitis treated soon after the introduction of penicillin found an incidence of penicillin-resistant *Staphylococcus aureus* of 4 % or less Wickström *et al* [13] reported an incidence of 6.5 % penicillin resistant organisms in their cases prior to 1949 and 30.6 % thereafter to 1953 Cullen & Glass [3] reviewing ?06 cases from this hospital found an incidence of 12 % and Salz [9] reported an incidence of 21 % over a ten-year period Harris [6] found 1? organisms of 3? recovered during a seven-year period to 1958 to be resistant to penicillin, an incidence of 37.5 %

The incidence of penicillin resistant organisms in this series which covers the two years 1958 and 1959 is 54.5 %

Cullen & Glass [3] and Harris [6] have shown that the incidence of complications rises if effective treatment is delayed Results in this series confirm this

TABLE 5. *Infections by penicillin-sensitive organisms*

Name	Age: yrs	Age: mths	Sex	Site	Source of organism	No. of days symptoms prior to treatment	Initial therapy	Progress and complications	No. of days stay in hospital
M. H.	10	9	F	Femur	Skin sepsis	3	Oral penicillin 3 days prior to admission. Dosage not known. Penicillin ½ mega* 6 hrly 28 days	No complications	42
R. G.	7	8	M	Tibia	Pus	3	Oral penicillin 60 mg 4 hrly for 24 hours prior to admission. Penicillin ½ mega twice daily 3 days. Tetracycline 21 days	Abscess drained 7th day and in 4th month. No further complications	173
A. M.	9	6	M	Radius	Skin sepsis	3	Parenteral penicillin 1 mega prior to admission. Penicillin ½ mega 6 hrly 21 days	No complications	31
K. W.	11	10	M	Os calcis	Pus	7	Penicillin 1 mega immediately. ½ mega 6 hrly 3 days. Tetracycline 21 days	Abscess drained 3rd day. No further complications	30
P. W.	2	4	M	Tibia	Blood culture	3	Penicillin ½ mega twice daily 21 days	Abscess drained 4th day. No further complications	28
C. M.	10	1	F	Femur	Urine culture	3	Penicillin ½ mega 6 hrly 3 days. ½ mega twice daily 24 days	No complications	130
J. B.	12	10	F	Femur	Blood culture	3	Penicillin ½ mega 6 hrly 3 days. Tetracycline 21 days	No complications	48
H. B.	14	0	M	Humerus	Blood culture	3	Tetracycline 28 days	No complications	31
D. B.	3	3	M	Femur	Pus	3	Penicillin ½ mega 6 hrly 24 days	Abscess drained 2nd day. Sequestrectomy and pathological fracture	480
B. Y.	14	1	M	Clavicle	Pus	3	Penicillin 1 mega twice daily 1 day. Tetracycline 21 days	Abscess drained 10th day. No further complications	23
L. W.	7	4	F	Femur	Pus	3	Penicillin ½ mega twice daily 3 days. Tetracycline 27 days	Abscess drained 5th day. Sequestrectomy	173
R. A.	6	0	M	Femur	Blood culture	3	Penicillin ½ mega twice daily 5 days. Oral penicillin 240 mg 6 hrly 16 days	No complications	35
K. O.	13	2	M	Ilium	Blood culture	5	Tetracycline 21 days	No complications	37
I. T.	8	6	M	Tibia	Pus	4	Penicillin ½ mega 6 hrly 3 days. Tetracycline 33 days	Abscess drained 7th day. No further complications	79

* 1 mega = 1 000,000 units.

The proportion of cases treated early or late in Groups 1 and 2 is approximately the same but when penicillin was given at the onset of treatment, the complication incidence was 54 %, whereas when tetracycline was given the incidence fell to 15 %. Penicillin is obviously ineffective in many cases of osteomyelitis, the clinical response confirming the bacteriological findings.

Usually two or three days elapse before the sensitivities of an isolated organism can be determined and it is important that this waiting period should not be wasted. A broad-spectrum antibiotic e g tetracycline should be given to all children with osteomyelitis as soon as the diagnosis has been made on the clinical findings. When an organism is recovered the antibiotic indicated by laboratory investigation can be used.

The majority of the children in this series appeared to tolerate well a three to four week course of tetracycline without troublesome side-effects. This agrees with the findings of de Romana *et al* [8] in their series of children suffering from osteomyelitis treated with a tetracycline-oleandomycin mixture

Summary

Fifty-eight children with acute haematogenous osteomyelitis have been studied. The incidence of infection by penicillin-resistant organisms was found to be 54.5 % in 33 cases in which an organism was recovered Tetracycline has been found to be more effective than penicillin in the primary treatment of this condition

Acknowledgements

The authors wish to thank Dr A. Holzel and Dr L. Parker for their help and advice and Dr W H Patterson for permission to include in this series a patient treated by him.

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Dept of Orthopaedic Surgery
The Royal Infirmary
Manchester 13
England

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From the Swedish Medical Research Council Unit for Paediatric Haematology and the Department of Paediatrics, University Hospital, Uppsala, Sweden

Studies on Erythro-Kinetics in Infancy[1] I

A Modified One-Minute Alkali Denaturation–Precipitation Method for Haemoglobin F Determination Agreement with Spectrophotometric Method

by LARS GARBY and JEAN-CLAUDE VUILLE

In studies on radioiron kinetics in early infancy [3] attempts were made to measure the incorporation of the labelled iron into both newly formed haemoglobin A and haemoglobin F In healthy infants the amount of radioactivity that could be injected was limited for safety reasons. On the other hand, the total volume of any solution that could be measured in our well type scintillation counter was limited to 5 ml. In order to obtain a sufficient amount of isolated haemoglobin F for radioactivity measurements, the one minut alkali denaturation–precipitation method of Singer Chernoff & Singer [7] was considered to be the simplest and most efficient procedure However in the original method 5 ml of haemoglobin F containing filtrate corresponded to the amount of haemoglobin F present in only 0 1 ml of a 10 haemoglobin solution which was not sufficient to allow accurate radioactivity measurements in our experiments. An attempt was therefore made to ork with considerably smaller amounts of reagents thereby reducing the dilution

A comparison between the precipitation method of Singer *et al* and spectrophotometric measurements was made by Jonxis & Huisman [5]. In contrast to the original method of Singer *et al* the present method gives results in agreement with the spectrophotometric method

Methods

Blood samples were obtained by heel puncture and collected in heparinized 3 ml tubes. In order to obtain a sufficient amount of blood (2–3 ml) the skin was covered beforehand with a thin layer of a silicone l bricant, a procedure facilitating the collection of blood from the puncture The samples were centrifuged for 5 minutes at about 1000 *g* the plasma and the leucocyte layers discarded, and the red cells washed once with 1 0% saline and haemolyzed by adding distilled water to give total volume of about ml. Toluene was then added (about half the volume of the packed red cells) and the tube was then shaken vigorously for 5 minutes and thereafter centrifuged for 20 minutes about 1500 *g* Finall the lear haemoglobin solution was sucked up int pipett and filtered through small filter paper Af er dilution of 0 1 ml of this sol tion with 25 ml of 0 4 NH OH, the haemoglobin concen ration w determined t 540 mμ in Beckma B spectrophoto-

[1] This ork was supported by grant from he Swedish Medical Research Council

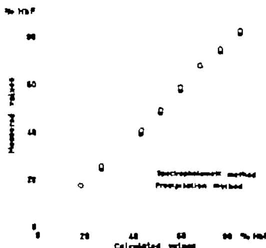


Fig 1 Agreement between the two method of measuring the relative concentration of HbF

meter A series of haemoglobin solution with varying haemoglobin F concentrations was prepared by mixing haemolysates of cord blood and of blood from a normal adult

The foetal haemoglobin was isolated as follows. Two millilitres of NaOH were placed in a 10 ml centrifuge tube and 0.50 ml of the haemoglobin sol ition added, rinsing the pipette al times. A stop-watch was started as the addition of haemoglobin began, and fter exactly one minut the denaturation process wa stopped by ad ling 4 ml of the precipit ting solution (800 ml 50 saturated ammonium sulphat acidified with 2 ml 10 N HCl) The tube was in verted several times and the mixture filtered through a double layer of filter paper To obtain a final dilution of 1 51 0.. ml of the filtrat was mixed w th 2.60 ml 0.4 NH OH and the optical lensity read at 540 mμ By d 'iding thi value by the optical density of the initial haemoglobin sol tion, the haemoglobin F concentration wa obtained

The spectrophotometric letermination of the foetal haemoglol n was performed a lescribed by Jon s & \ ser [4].

Result

Duplicate determination were performed on 31 samples with HbF concentrations between 1 and 8. . From the differences of the results of the duplicate determinations, the coefficient of variation of a single determination wa found to le 1 4 of the mean value in the range 50-85% HbF 1 0 in HbF concentrations between 15 and 50 and 8 in samples containing less than 15 HbF

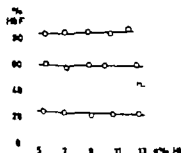


Fig 2. The relative concentration of HbF at different concentrations of tot l haemoglobin.

Fig 1 shows the concentration of foetal haemoglobin in an artificially prepared series containing varying amount of HbF as determined both by our modified method and by spectrophotometric determinations. As can be seen there is good agreement between the result of the two methods in the range 10-85 HbF the differences not being greater than the error of a duplicate determination with a single method.

In the radioactivity mea urement of the haemoglobin samples the volume of the initial solution had to be the same for every sample in order to avoid errors resulting from different geometrical f ctors in the detector As the q ntity of red cells obtained by heel puncture wa not always the same and a it wa desired to use all available haemogl for th radioactivity mea urement t wa not pos ible to keep the concentration of haemoglobin in the init l solut n con

stant In fact it varied from 6 to 13 g %. To determine whether this considerable variation could influence the results of the HbF isolation to a significant degree solu tions containing different amounts of HbF were prepared as described above The HbF concentration in different dilutions of these mixtures was then determined with our modified method. The results, as shown in Fig * indicate that there is no significant difference within the range 5 to 13 g %

Discussion

A modification of the one minute alkali denaturation–precipitation method for the determination of HbF in the blood of young infants has been introduced in order to get a greater concentration of HbF in the final filtrate. This is of importance when small amounts of radioactive iron in HbF have to be measured with sufficient precision. By reducing the volumes both of the denaturating and the precipitating solutions we obtained a four fold increase in the concentration in the filtrate, as compared with the original method of Singer Chernoff & Singer [7].

Jonxis & Huisman [5] comparing the results of HbF determinations by the spectrophotometric procedure with those obtained by the one-minute precipitation method, concluded that the former gave more reliable results, as the spectrophotometric values were in good greement with the calculated ones in mixtures of purified HbF and HbA The precipitation method however gave consistent results only in samples containing 40–60 % HbF wherea the values were too low in higher HbF concentrations and too high in concentrations below 40 %. The cause of this discrepancy is not known, but Betke [1] has pointed out that the alkali-induced altera tions of the haemoglobin molecule which lead to a decreased solubility are probably not identical with nor do they proceed at the same rat as those which are responsible for the changes in the spectral absorption.

Singer Chernoff & Singer [7] in accord ance with earlier investigators (Brinkman & Jonxis [ ]; Ponder & Levine [6], and others) pointed out the importance of the pH of the reaction mixture a lower pH resulted in a decrease in the denaturation rate of the adult haemoglobin, thus giving an overestimate of HbF levels in adult blood. It is obvious that our modification introduces conditions that are different from those of Singer *et al* the fourfold increase in th amount of haemoglobin must have decreased the pH by dilution and buffering though we used exactly the same reagents as these uthors The alkali resistant fraction in haemoglobin solutions from five adult donors, determined by our method, is probably somewhat higher (1 1–2.2 %) than those obtained by Singer *et al* (0 0–1 7 %). Our method cannot perhaps be recommended therefore for the estimation of small amounts of HbF but when dealing with concentrations between 10 and 90 %, this possible source of error may be regarded a negligible In actual fact comparison with spectrophotometric measurement showed that our modification gave more consistent results than the original method It is difficult to xplain th improvement, which was only a hance discovery since the investigation was ndertaken for ther reason. It i possible that n the original method the

higher pH is responsible for a too fast denaturation of the HbF in concentrations above 60 % and on the other hand the dilution of the haemoglobin by the reagents may be too great resulting in an incomplete precipitation of the HbA in samples containing less than 40 % HbF

The reproducibility of the present method, the coefficient of variation between 1 4–8 % depending on the concentration of HbF present is comparable with that of the method of Singer *et al* and satisfactory for many studies. The method gives consistent results in samples with total haemoglobin concentrations ranging from 5 to 13g %, which is also in agreement with the findings of Singer *et al*

Summary

The one-minute alkali denaturation-precipitation method for HbF determinations of Singer Chernoff & Singer has been modified to give a fourfold increase in HbF concentration in the filtrate With this modification the denaturation precipitation method shows good agreement with measurement based on spectral absorption changes The method gives reproducible results within a considerable range of HbF and total Hb concentrations

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Department of Pediatrics
University Hospital
Uppsala
Sweden

CASE REPORT

The Treatment of Aplastic Anaemia with Anabolic Steroids

by MOSTAFA KHALIL and ABDEL-HADI IBRAHIM

From the Department of Pediatrics (Head: Professor A. S. Abbassy), University of Alexandria, Egypt, U.A.R.

The treatment of aplastic anaemia has so far been a very unsatisfactory haematological problem. Haematinics of all kinds, stimulating doses of X rays to the bone marrow, adrenalin, corticosteroids and other factors have all been extensively tried with very doubtful values. Repeated transfusions, preferably with concentrated suspensions of fresh red cells, which also contribute fresh platelets, have until now been the most beneficial line of treatment.

In 1959 Shahidi & Diamond published the encouraging results they obtained after treating five children suffering from aplastic anaemia with a combination of corticosteroids and testosterone. The present paper demonstrates the results of our experience of adopting a modified course of combined anabolic steroid and corticosteroid therapy on two girls suffering from the disease.

Case 1

M. N., a girl aged 5½ years. She was admitted to hospital complaining of severe pallor, bleeding gums, purpuric eruptions, weakness and easy fatiguability for a period of 2½ months. The condition started with the appearance of anaemia, for which the patient was given liver extract injections. She developed gluteal abscess, which was incised and resulted in profuse bleeding. There was no history of exposure to irradiation or of intake of a drug toxic to the bone marrow.

On examination the general condition of the child was very bad. She was drowsy and showed severe pallor. The pulse was 130/min and the blood pressure 110/50. Purpuric spots were scattered all over the body, the sternum was not tender, the spleen was not felt and there was no enlargement of lymph nodes. A faint apical systolic murmur was heard.

The urine and stools were normal. Blood examination showed pancytopenia. A myelogram demonstrated definite evidence of …plasia of all the three elements of the blood and the case was diagnosed as aplastic anaemia.

The child was put on corticosteroid therapy (Millicorten, Ciba) for three weeks, but no improvement resulted and blood transfusions had to be given every four or five days for a period of three months. During this time the girl was hardly ever free from echymotic and purpuric patches. The blood picture was as follows: Haemoglobin 8 g/100 ml, R.B.C. 2,100,000/mm³, W.B.C. 2900/mm³ (polymorphs 1000/mm³, lymphocytes 1,600/mm³), platelets 30,000/mm³, reticulocytes 0.03%.

A combination of Millicorten and Ultandren[2] (Ciba) was then started. Four mg of

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[1] Dexamethasone (16α methyl-9α-fluoro-prednisolone).

[2] Fluoxymesterone (9α-fluoro-11β-hydroxy-17α-methyl testosterone).

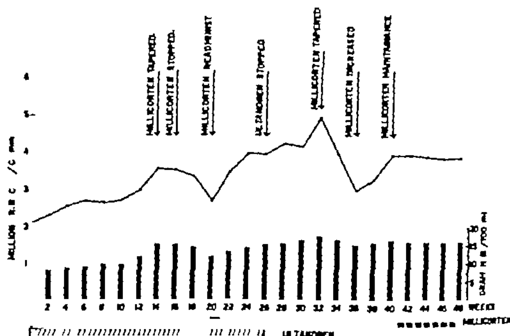


Fig. 1. The effect of treatment on the red blood cell count and haemoglobin content.

Millicorten + 4 mg of Ultandren were given daily for two weeks. The dose of Millicorten was thereafter diminished first to 3 mg and then to 2 mg every day and that final dosage was continued for a period of 11 weeks. No blood transfusions were given after the beginning of this treatment.

It is clear from Fig. 1 that the haemoglobin content and red cell count progressively improved t levels of 15.5 g/100 ml and 3 630 000 red cells/mm³. The general condition of the child improved markedly and she put on weight. The improvement in the platelet level was similarly obvious and the count ranged from 85,000 to 100,000 per mm³. Purpura completely disappeared. The effect of treatment on the whit blood cells was, however not so rewarding. The total leucocytic count showed a slight rise but with fluctuation from a level of 2300/mm³ at the onset to a maximal count of 4500/mm³. Out of these the lymphocytes before treatment were 1700/mm³ and became 2000/mm³ and the polymorphs were 1000/mm³ and became 1800/mm³ (Fig. 2). Examination of the bone marrow demonstrated an active tissue with extensive normoblastic reaction but moderate hypoplasia of the white series.

At this stage it was thought desirable to study the effect of gradually withdrawing corticosteroids and maintaining the child on Ultandren. This was carried out and corticosteroids were completely stopped after two weeks. As is shown in Fig. 1 the haemoglobin level and the red cell count progressively dropped to 12 g/100 ml and 2,790,000 mm³. The platelets similarly reached a level of 30 000/mm³ within a period of four weeks and purpura and echymotic patches once more ppeared all over the body. The white cell count also diminished to total of 3200/mm³.

At that point corticosteroids were again reinstituted in the same order as first administered and a second improvement in blood cell count and haemoglobin content was achieved. The following figures were

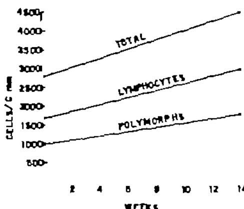


Fig. 2. The response of white blood cells t treatment during the first 14 weeks.

arrived at seven weeks after reinstitution of the combined therapy: Haemoglobin 15.5 g/100 ml, R.B.C. 4,460,000/mm³ W.B.C 4400/mm³ (polymorphs 1100/mm³), platelets 100,000/mm³

In order to verify the degree of recovery of the bone marrow measurements of ferrokinetics using Fe^{59} were then made. These can be used to trace the sequential movement of iron from the plasma, through the bone marrow liver spleen and red cells. The method of Pollycove & Mortimer [7] was used

(1) 14 ml of fresh plasma labelled with 20 microcuries Fe^{59} were injected intravenously

(2) Blood samples were then taken 30 minutes, 55 min tes, 75 minutes, 24 hours, four days, eight days and 14 days later and analysed for plasma and erythrocyt radioactivity

(3) Haematocrit values were then determined on ll samples.

(4) Serum iron was estimated using the method of Peters *et al.* [6].

(5) Surface measurements of radioactivity over the liver spleen and sacral bone marrow were made and plotted as a ratio t zero time radioactivity when all radioactive iron was still in the plasma, i.e. immediately after injection. Count were therefore taken t zero time and then after one hour four hours, 24 hours, four days, six days, nine days and 14 days.

Applying the formulas and mathematical models of Pollycove [8] the following normal results were obtained.

Serum iron 123.0 µg/100
Haematocrit 45
Plasma volume 1584 ml
Blood volume 2732 ml
R.B.C. vol me 1148 ml
Amount of iron in plasma 2 00 mg
Plasma iron turn-over 18 05 mg/day
Amount of iron in the labile iron pool of the bone marrow 45.3 mg
R.B C. iron turn over 10.65 mg/day
Daily haemoglobin formation 3 13 g
Mean erythron lif span 122 days
Body weight 30 kg

Figs. 3, 4 and 5 show the results of our study w th Fe^{59} As is shown, radioactive iron moved rapidly from the plasma t the bone marrow remaining there for a mean haemoglobinisation time of 1.5 days. For the next four days gradual discharge occurred with simultaneou appearance in the circulating erythrocytes. In the plasma there was a rapid drop of radioactive iron for two days, followed by a much slower one

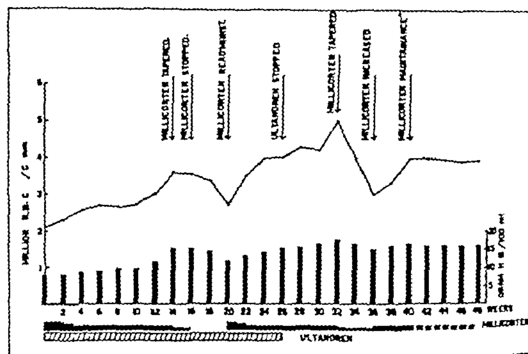


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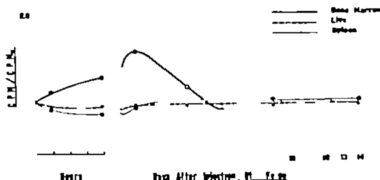


Fig. 5. Surface radioactivity (normal pattern). C.P.M./C.P.M.$_0$ = counts per minute/counts per minute at zero time.

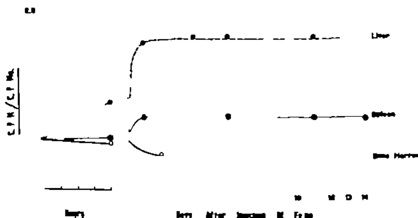


Fig. 6. Surface radioactivity (showing evidence of bone marrow hypoplasia).

the blood picture It was therefore readministered and the condition improved again. W finally decided t keep the child on an interrupted maintenance dose of Millscorten and she was therefore scheduled on a four days-a week course of 2 mg a day The blood picture for two months has been satisfactory

Case 2

A M 9 year old girl who was admitted t hospital complaining of purpuric and echymotic patches on the face and upper limbs of only a few days duration. There was no history of previous similar ttacks or any drug intake

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(M. K.) 22, East Port Street
Saad Zaghloul Square
Alexandria
Egypt
U.A.R.

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REVIEW ARTICLE

Congenital Ataxic Syndromes in Cerebral Palsy[1]

by T T S INGRAM

Department of Child Life and Health, University of Edinburgh, Scotland

French pathologists were interested in children with abnormalities of the cerebellum from the early years of the 19th century (Combettes 1830 Lallement 1862). A large number of cases of congenital cerebellar agenesis and hypoplasia were presented in his superb monograph on the cerebellum by André Thomas in 1897 These reports were sufficient to indicate that severe cerebellar hypoplasia and even agenesis were not necessarily associated with gross neurological disability but the early interest was shown predominantly by neuroanatomists and neuropathologists

Clinical interest in cerebellar disorders in childhood may be said to date from the time of Friedreich who published his first paper on the "familial spino-cerebellar degeneration which bears his name in 1861 and continued to amplify his original description and add further cases in papers written in 1863 and 1876 The classical signs of his syndrome were pes cavus, intention tremor nystagmus slurred speech, hypotonia and diminished or lost tendon jerks Initially neurologists and particularly Charcot and his followers did not accept that Friedreich had described a new disease but thought that his patients suffered from multiple sclerosis or amyotrophic lateral sclerosis at an unusually early age In the next two decades however other authors also found patients similar to those which Friedreich had described and "Friedreich s disease" became accepted as a distinct clinical entity (Gowers 1880, 1888)

The result of Friedreich s work was to stimulate interest in other forms of ataxia in childhood. In particular patients were described who showed progressive spinocerebellar ataxia with exaggerated tendon jerks especially in the lower limbs. Others were presented in whom the neurological disorder appeared to date from birth and was not progressive A number of such case reports were collected and studied by Freud, 1893, 1897 In the earlier work he described two patients with intention tremor nystagmus and taxia dating from birth or shortly afterwards and speculated as to whether they were congenital examples of Friedreich disease or whether they represented an ataxic form of congenital cerebral palsy In 1897 he discussed the possible need for a special category of ataxi cerebral palsy" in the future but felt that up to

[1] Based on lecture given under the auspices of the Folke Bernadotte Foundation in Gothenburg, Uppsala and Lund, May 1961

his time too few cases had been described to make this necessary

Six years after Freud s suggestion that a category of "ataxic cerebral palsy" might be required Batten of St Bartholomew s Hospital in London described eight children with congenital ataxia or cerebellar diplegia" In three of them there was a history of abnormal labour or delivery Slow motor development defective speech and unsteadiness were the presenting clinical features. On examination there was marked unsteadiness, incoordination of the limbs intention tremor and in some nystagmus All but one of the patients were hypotonic though in some of them the tendon jerks seemed brisk rather than diminished Batten emphasised that ataxic patients improved as they grew older and that independent walking without support was almost always achieved He thought that congenital ataxia could be the result of damage to the cerebellum at the time of birth but that in other cases it was the result of developmental malformations of the brain. The Sister in Hope Ward in St. Bartholomew s Hospital had a half Persian cat who had an ataxic kitten and Batten [2a] was interested to find at autopsy that its cerebellum was hypoplastic

Batten also realised that ataxia in childhood could be acquired as a result of encephalopathies complicating infectious disease and by intracranial abscesses and tumours. In 1905 [16] he distinguished between congenital cerebellar ataxia, ataxia acquired as a result of acute illness— encephalitis cerebelli —and progressive cerebellar ataxia of which Friedreich s disease was one type

By his descriptions of congenital and non progressive acquired ataxia in childhood Batten established the existence of "ataxia as a category of cerebral palsy and other patients were soon reported [16 27]

Descriptions of four more cases of cerebellar ataxia were given by Förster [7]. He thought these differed somewhat in their clinical findings from those previously presented and called them examples of atonic astatic infantile cerebral palsy As babies they showed striking poverty of movement gross hypotonia and undue passive mobility of all joints. All four children proved to be mentally defective as they grew up and as well as being very retarded in motor development were extremely slow to speak, two still being mute at the age of three years. They were unable to maintain postures, though voluntary movements appeared to be little short of normal power All movements, however were very incoordinate and intention tremor was present. Förster suggested that the condition was not directly attributable to cerebellar disease for in two similar cases which had come to autopsy he had found atrophic sclerosis of the frontal lobes. He considered that there were transitional syndromes between "atonic astatic infantile cerebral palsy and cerebral diplegia for some patients with marked inco-ordination of the limbs showed increased tone and increased tendon jerks with extensor plantar responses.

Further patients similar to those described by Batten in 1903 and by Forster were presented by Clark [4] 1913 Clark added little new to the clinical picture of atonic astatic infantile cerebral palsy He attributed the condition to develop-

mental malformations in most cases. Reports of the clinical findings were such that it was impossible to explain them on the basis of cerebellar abnormalities only and he postulated that there must also be abnormalities in the cerebral hemispheres. Like Förster Clark described a number of transitional clinical syndromes in which inco-ordination of voluntary movement intention tremor and unsteadiness were associated with spastic increase of tone in the lower limbs, exaggerated knee and ankle jerks and extensor plantar responses. More descriptions of patients with ataxic cerebral palsy some of whom showed persistent muscular hypotonia and hyper-extensibility nd others of whom had spastic increase of tone in the lower limbs with increased tendon jerks and extensor plantar responses, were reported by Batten & von Wyss [3] Parkes Weber [28], Hunt [19] and more recently by Phelps [24], Perlstein [23], and Horton & Yarnet [18] but it cannot be said that these recent reports have added very much to the knowledge of ataxic syndrome. In particular there is still a great lack of accurate recent information about the neuropathology of congenital ataxic disorders in childhood.

TABLE 1 *Classification of cases of cerebral palsy in childhood*

	Neurological diagnosis	Distribution
	Hemiplegia	Right Left
	Bilateral hemiplegia	
	Diplegia	
	Hypotonic	Paraplegic
	Dystonic	Triplegic
	Rigid or spastic	Tetraplegic
	Ataxic diplegia	
	Hypotonic	Paraplegi
	Spastic	Triplegic
Ataxic syndromes	With contracture	Tetraplegic
	Ataxia	
		Mainly unilateral Bilateral
	Dyskinesia	
	Dystonic	Monoplegic
	Choreoid	Hemiplegic
	Athetoid	Triplegic
	Tension	T traplegic
	Tremor	
	Other types	

Classification of Ataxic Disorders n Cerebral Palsy

Analysis of published case reports allows the definition of two major categories f taxic cerebral palsy (Table 1) They are shown together with the other categories of cerebral palsy defined in a recent neurological classification in T ble 1 (Ingram [20]) In the first of these which is best called simply taxia there is persistent hypotonia dating from birth. Affected babies show marked poverty of spontaneous movement severe retardation of motor development and are usually slow to speak. When they do sit or walk they are unsteady and they walk with their legs wide apart and flat footed. They tend to use their arms to help them to balance and when they reach for objects they show intention tremor Their speech is usually slow and slurred. On examination they show unsteadiness, intention tremor inco-ordination of voluntary movement dysdiadochokinesis hypotonia and sluggish tendon jerks. The plantar responses are usually flexor

The second category of taxic cerebral palsy is conveniently called ataxic diplegia for there are some of the features of spastic diplegia associated with the ataxia Initially affected babies show a lack of

TABLE 2 *Comparison of findings in children with ataxic diplegia and ataxia*

	Ataxic diplegia	Ataxia
Gait	Less broad-based On the toes	Very broad based Flat-footed
Muscle tone	Spastic especially in lower limbs	Hypotonic
Tendon jerks	Always exaggerated especially in lower limbs	Usually sluggish
Plantar responses	↑ ↑	Usually ↓ ↓
Later contractures	Frequent	Never
Epilepsy	Quite frequent	Infrequent

spontaneous movement and are hypotonic like those with ataxia, but after a period of weeks or months other clinical features become apparent. In particular it becomes evident that there is paresis of voluntary movement as well as inco-ordination This paresis is accompanied by spastic increase of tone in all the limbs but is more marked in the lower limbs than the upper The tendon jerks are increased especially in the lower limbs and the plantar responses are extensor *When these children* finally walk which may not be until they are four or five years of age or even older they walk on their toes, not flat-footed They keep their legs closer together than patients with ataxia and there is sometimes some scissoring of the legs, though this is hardly ever as severe as it is in spastic diplegia or Little's disease Patients with ataxic diplegia are liable to develop flexor contractures at the hips and knees with contractures in plantar flexion at the ankles. Contractures are never found in patients with ataxia In short, there is evidence of what used to be called pyramidal involvement in ataxic diplegia and this is not found in ataxia. This may suggest that there is greater cortical involvement in ataxic diplegia than in ataxia and may possibly explain why epilepsy is relatively frequent in ataxic diplegia and infrequent in ataxia (Table 2)

The Prevalence of Ataxic Cerebral Palsy

Ataxia and ataxic diplegia are the most often misdiagnosed forms of cerebral palsy [17] Children with ataxia are often considered to be mentally defective or to suffer from muscular dystrophy or amyotonia congenita or mild choreoathetosis.

Patients with ataxic diplegia are commonly misdiagnosed as suffering from spastic diplegia, spastic tetraplegia or Little's disease and their ataxia is missed. Others are considered to be mixed cases of cerebral palsy or are suspected of having tumours of the cerebellum.

Because of differences in the bases of classification it is difficult to be sure what proportion of patients suffer from ataxic cerebral palsy In a recent hospital series of 370 patients suffering from cerebral palsy Skatvedt [25], found that 6 5%

were ataxic and that ..3 % suffered from mixed cerebral palsy Andersen [1] in a regional survey carried out in Østfold County placed 11 7 % of patients in his category of "ataxia and an additional 13 % of patients were noted to have tremor In Stockholm 6 % of patient were considered to be ataxic and 8.5 % to suffer from mixed forms of cerebral palsy [6]. In an Edinburgh survey [*0] 5 7 % of patients were classified as suffering from ataxic diplegia and 7.. % as suffering from ataxia, giving a total of almost 13 %. Amongst 700 children suffering from cerebral palsy seen in two Edinburgh clinics in the last four years, 85 patients have been diagnosed as suffering from ataxia or ataxic diplegia—approximately 1 %. Seventy two of these patients have been studied in sufficient detail to make clinical analysis worth while Sixty had never been normal since the time of birth and were considered to suffer from congenital ataxia or ataxic diplegia In 11 patients the ataxic syndrome was considered to be acquired, usually as a result of cute infectious disease or trauma

Clinical Findings in Congenital Ataxic Diplegia and Ataxia

Aetiology

Compared to other forms of congenital cerebral palsy rather a small proportion of patients who were in both categories were born after abnormal pregnancy labour and delivery Fifty two per cent of patient with ataxic diplegia and 48 .. of those with ataxia were delivered spontaneously after apparently uncomplicated pregnancies and labours In many of the others there were only minor abnormalities of pregnancy or labour and delivery which were not considered to be of great significance but in 1 % of patients with ataxic diplegia and in 19 of those with congenital ataxia there were multiple disorders of pregnancy or labour and delivery The commonest abnormalities of pregnancy were pre-eclamptic toxaemia and antepartum haemorrhage The most frequently occurring disorders of labour and delivery were uterine inertia or obstructed labour breech extraction and forceps delivery (Table 3) Nineteen of the 33 patients with congenital ataxic diplegia were well immediat ly after birth and no abnormality was noted in the immediate neonatal course Ten were apnoei immediately after delivery in three cases for longer than five minutes. Nine patients were considered to show signs of "birth injury in the neonatal period Five of these had generalised seizures, all of which occurred within the first week of life and four of them were noted to be tense restless excitable babies who cried easily and fed with difficulty Similar behaviour without seizures was observed in another three of the infants.

Seventeen of the 27 patients with congenital ataxia appeared to be quite normal immediately after birth and were not considered to show signs of brain damage or abnormality in the neonat l period Five were apnoeic immediately after delivery two for longer than five minutes and three breathed at once but were observed to have associated congenital malformations immediately after delivery Only four patients with congenital ataxia were noted to be abnormal in the first week of life Two suffered from intracranial haemorrhages and two from cyanotic attacks one as a result of associated con

TABLE 3 *Percentage distribution of 60 patients with congenital ataxic diplegia and congenital ataxia by abnormality of pregnancy labour and delivery*

	No. of patients	Abnormal pregnancy only %	Abnormal labour and/or delivery only %	Abnormal pregnancy and/or labour/ and/or delivery %	Σ abnormality of pregnancy labour or delivery %
Congenital ataxic diplegia	33	15	15	31	61
Congenital ataxia (1 unknown)	27	22	11	10	43

genital heart disease and the other following operation for the removal of an occipital meningocele

The fact that as many as two-thirds of patients in both categories were born after apparently uncomplicated pregnancy labour and delivery and were not considered to show any signs of birth injury to the brain in the neonatal period suggests that birth injury may be of less aetiological importance in ataxic syndromes than in some other types of cerebral palsy On the other hand, birth injury seems to have occurred in at least a minority of patients for approximately 20 % were born after multiple disorders of pregnancy and labour 25 % were apnoeic after delivery and a significant proportion (27 %) of patients with ataxic diplegia had indications of acute brain disease in the neonatal period.

Some evidence was obtained which was in favour of developmental malformations being responsible for ataxia and ataxic diplegia in at least a proportion of cases. Older mothers are known to have more birth injured children and also more babies with developmental malformations than younger mothers. Thus the finding that more than 50 % of the patients were born to mothers over the age of thirty in itself has no great significance but further analysis showed that more mothers under the age of thirty in both categories, had ab-

TABLE 4 *Patients with congenital ataxic diplegia and ataxia by age of mother and normality of pregnancy labour and delivery*

Maternal age		No. of cases	Uncomplicated pregnancy labour and delivery %	Abnormal pregnancy labour and/o delivery %
Ataxic diplegia	Mothers under 30	17	47	53
	Mothers over 30	16	57	43
Ataxia	Mothers under 30	11	27	73
	Mothers over 30	14	60	40

Full information lacking in 2 of 60 patients.

TABLE 5 *Fate of the pregnancies of mothers with children suffering from congenital ataxic diplegia and congenital ataxia*

	Congenital taxic diplegia (33 mothers)	Approx. %	Congenital ataxia (26 mothers)[a]	Approx. %
Number of pregnancies	113	—	0	—
Number of offspring (including twins)	115	100	4	100
Abortions	9	8	3	4
Stillbirths	1	1	2	2
Infant deaths	3	3	2	3
Abnormal siblings (surviving)	4	4	2	4
Patients	33	29	27	36
Healthy children	65	85	37	80

[a] Full information lacking in one of 27 patients.

normal pregnancy labour and or delivery than older mothers—a reversal of the expected trend It seems possible that there is a tendency for younger mothers to produce children with ataxia and ataxic diplegia because of birth injury whereas older mothers may produce them because of their greater tendency to have children with developmental malformations (Table 4)

It may also be shown that the mothers of patients with ataxia and ataxic diplegia have *slightly fewer pregnancies than* mothers in the general population of Scotland, though they are in fact slightly older and that many of their pregnancies are un successful (Table 5) Rather a high proportion of pregnancies result in abortion, still birth or in the delivery of babies who die in infancy or show developmental abnormalities. When the patients are inclu ded in the calculation, it is found that only about half the pregnancies result in the birth of healthy children.

Another point in favour of developmental malformations being a cause of ataxia and ataxic diplegia is the fact that girls suffer from both disorders significantly more often than boys—*the ratio being* approximately six to four in both categories Whereas birth injury invariably affects boys more commonly than girls, some developmental abnormalities of the central nervous system are known to be commoner in the female than the male

The finding that 15% of patients with ataxic diplegia or ataxia weighed 2500 g or less at birth is also compatible with a significant proportion of cases being the result of developmental malformation Murphy [22] found that 18 3 % of 934 malformed children were prematurely born compared to 4% of 1040 of their normal sibs. In fact 40% of patients with ataxic diplegia and ataxia showed associated developmental anomalies of the nervous system or of other parts of the body hypertelorism being present in four spina bifida in four congenital heart disease in one congenital cataract in two and other malformations in four patients.

How often congenital ataxia and taxic diplegia are the result of genetically deter mined malformations and how often the

TABLE 6 *Family history of 33 patients with congenital ataxic diplegia and 27 with congenital ataxia*

	Cerebral palsy	Epilepsy	Mental defect	Other congenital abnormality	
Congenital ataxic diplegia					
Aunts and uncles	3	2	2	0	11 patients 33 %
Parents	0	1	0	2	
Surviving sibs	1		1	0	
Congenital ataxia					
Aunts and uncles	0	1	1	1	7 patients 25 %
Parents	0	0	0	1	
Surviving sibs	0	0	0	3	

result of malformations originating in early pregnancy as the result of teratogenic influences is impossible to estimate There is no doubt that ataxic diplegia and ataxia may occasionally be genetically determined. Two of the ataxic patients in the present series were brothers and I have examined one patient with non-progressive congenital ataxic diplegia whose sister mother maternal uncle maternal grandmother and maternal great grandmother all almost certainly suffered from an identical condition. It is unusual to get such clear evidence of heredity however and it is difficult to interpret the finding that a relatively high proportion of patients sibs, parents and uncles and aunts had neurological disorders of different types (Table 6)

The Course of Ataxic Diplegia

Apnoea, generalised seizures in the first week and "cerebral behaviour" are transient phenomena in the minority of patients with ataxic diplegia in whom they occur When they have disappeared, the majority of patients are not strikingly abnormal. If the patient is the first child the parents often notice nothing wrong for weeks or even months. Commonly it is only when the grandmother or some other experienced relative observes that the child is retarded in development that abnormality is suspected.

Twenty per cent of parents first complained to doctors about their baby's floppiness" or lack of movement within the first six months of birth. Epileptic attacks were the first sign of abnormality in another 12 % before this age. In patients with hydrocephalus the size of the head was usually the first abnormality which the parents noted, but in the majority of patients it was retarded development of head control and independent sitting which attracted attention. In fact, motor development is extremely retarded and half the patients could still not sit without support by the age of eighteen months and 46 % could not walk even when they were four years of age Speech development is also very retarded and much more delayed than in other forms of cerebral palsy even when allowance is made for the mental defect of many cases (Table 7).

TABLE 7 *Ages at which 33 patients with congenital ataxic diplegia first sat unsupported, walked unsupported and said their first phrases*

Sitting			Walking			Phrases		
Age months	No. of patients	Average intelligence	Age years	No. of patients	Average intelligence	Age years	No. of patient	Average intelligence
0–12	8	(5 average)	0 2	5	(All average)	0–	3	(All average)
12 18	8		2 3	8		2 3	7	
18+	17	(2 average)	3–4	5		3–4	5	
			4+	15	(1 average)	4+	18	(0 average)
All ages	33		All ages 33			All ages 33		

On examination in the first weeks of life it is impossible to distinguish between patients who will later show ataxia and those who will later show ataxic diplegia though epileptic seizures in a hypotonic baby make it much more likely that it will suffer from ataxic diplegia than ataxia. Whether the later diagnosis is ataxia or ataxic diplegia, the babies will be immobile showing a striking lack of spontaneous movement of the head, trunk or limbs. When they are picked up head control is found to be extremely poor There is generalised hypotonia with hyperextensibility of all joints and often the fingers may be bent back so far that the nails touch the back of the wrist The Scarf sign ("signe de foulard") is almost invariably positive The tonic neck reflexes are absent grasp reflexes cannot be elicited nd reflex walking and the stepping reflex are commonly absent lso Even the Moro reflex may be very difficult or impossible to elicit Tendon jerks are absent or extremely sluggish Within ten or twelve weeks, however many patients with ataxic diplegia are rather less hypotonic and it i possible in many of them to elicit the knee jerks relatively easily by this time By the ge of about four months there may be definite spasticity in the lower limbs and the knee and ankle jerks can readily be elicited. As the spasticity increases so the hyperextensibility decreases.

When the child begins to reach for objects, which may be before he has full head control, intention tremor is usually very obvious and the gross inco-ordination of voluntary movement which is so typical is very apparent When the child does sit with support head tremor may be noted, especially when he looks from side to side When walking with support finally becomes possible gross unsteadiness and tendency to fall are obvious The gait varies ccording to the severity of the spasticity but children with ataxic diplegia always walk with their feet in the equinus position on their toes When the spasticity is mild, there is usually little adductor spasm and the legs are held wide apart When the spasticity is more severe there is more adductor spasm and the legs are held close together Most children with taxic diplegia walk with the hips lightly flexed and internally rotated, the knees semi-flexed and the feet slightly interned and in the equinus position They tend to circumduct each leg in turn in front of the

other and lean forward as they proceed with their arms abducted and slightly flexed at the shoulders, moving them up and down like balancing poles. Dwarfing of the pelvis and lower limbs in ataxic diplegia is usually slight when it occurs and never comparable in severity to that found in cerebral diplegia. Contractures are particularly liable to occur in ataxic diplegia particularly at the hips and knees.

By the age of three or four years a number of associated neurological abnormalities are apparent. About one-third of the patients are epileptic. Grand mal seizures are the commonest form of epilepsy but myoclonic jerks were found (twice associated with grand mal attacks) in three patients. These myoclonic jerks were sufficiently severe to throw the children to the ground when they occurred and in two cases were the major disability from which the child suffered. In two of the patients the myoclonic attacks responded to treatment with steroids. Mild hemiplegia associated with some dwarfing of the limbs on the affected side was present in three patients. Strabismus convergent in type except in one case was present in thirteen patients. Nystagmus occurred in only three. One child showed marked optic atrophy with very limited visual acuity two suffered from congenital cataracts. Spina bifida was present in two cases and four patients showed hydrocephalus which dated from birth or very shortly after. It is perhaps worth stressing that when hydrocephalus is associated with cerebral palsy it is almost invariably a picture of ataxic diplegia which is found.

Only one quarter of the patients was found to be of average intelligence. One third was mentally defective and the remainder were feeble-minded. These findings were reflected in the school placements of the children, 32 % being ineducable 46.5 % being educable only in schools for physically or mentally handicapped children and 21.5 % educable in schools with healthy children.

The Course of Ataxia

Parents of children with ataxia noticed their children were abnormal even later than parents of those with ataxic diplegia. This was partly because patients with ataxia did not have seizures in early infancy but it was remarkable that, though practically all the parents commented retrospectively on the marked floppiness of their babies, only two of them sought medical advice on this account at the time. In three cases congenital anomalies were noted within the first six weeks but in the great majority of ataxic patients it was retarded motor development—the child's inability to sit even with support even at a year—which made the mother seek medical advice. As with the patients suffering from ataxic diplegia all motor and speech milestones were very retarded (Table 8). Twelve of the patients were unable to walk by the age of three years and sixteen had no phrases by this time. Articulation was slow and defective when the children did eventually speak. When examined as babies, the patients invariably showed marked poverty of movement and poor control of posture. They were generally hypotonic with the same marked hyperextensibility of joints which was observed in ataxic diplegia but whereas the patients with ataxic diplegia gradually developed spastic increase of tone in the lower

TABLE 8. *Ages at which 27 patients with congenital ataxia first sat without support walked unsupported and said their first phrases*

Sitting		Walking		First phrases	
Age, months	No. of patients	Age, years	No. of patients	Age years	No. of patients
0–1	6	–	5	–2	2
1–18	13	2–3	10	–3	9
18+	4	3–4	6	3–4	8
Unknown	4	4+	6	4+	8
All ages	27	All ages	27	All ages	7

limbs those with ataxia remained generally hypotonic. When examined at the age of four or five years, they still show poor control of posture. They sit with round back and shoulders and the head thrust forwards, frequently showing considerable tremor of the head when they turn it to look at anything. When they reach for objects, intention tremor of the hand is obvious and usually symmetrical in its severity. There is always generalised hypotonia and in some cases hyperextensibility of the limbs may be almost as severe at this age as it was in infancy. Tendon jerks are almost always very sluggish but pendular responses may be obtained at the knees. The plantar responses are usually but not invariably flexor. When these patients walk, they keep their legs wide apart and their feet flat on the ground. Most of them take a step forward by throwing the leg forward and a little laterally from the hip often not taking the foot from the ground and, like the patients with ataxic diplegia they elevate the upper limbs at the shoulders and use them as balancing poles. They are extremely unsteady when they cannot compensate for their lack of balance by using their eyes but in spite of this the Romberg test considered so reliable in ataxic adults, is often negative.

Epilepsy is less common than in ataxic diplegia and in fact occurred in only two of the 28 patients, one of whom suffered from grand mal epilepsy and the other from myoclonic seizures. Associated hemiplegia was present in one patient but was mild in severity. Sixteen patients suffered from strabismus, but nystagmus was present in only two patients. Intelligence was found to be rather less severely impaired in ataxic patients than in those with ataxic diplegia. Thirty-six per cent were of average intelligence and 39% were able to go to school with normal children, but 21% were considered to be mentally retarded and of those of school age 32%, or about one-third, were considered to be ineducable.

In spite of the very retarded early motor development of many of these patients the prognosis for later physical activities is better than in other types of cerebral palsy. The compensation that some patients achieve for their disability is remarkable and it is not uncommon to find children riding bicycles at the age of fifteen or sixteen years who could not walk steadily until the age of four or five

Summary and Conclusions

Ataxic syndromes have attracted less attention in the past than other forms of cerebral palsy yet recent surveys suggest that more than 10% of patients with cerebral palsy are ataxic.

Analysis of case reports in the literature leads to the differentiation of two forms of ataxic cerebral palsy "Ataxic" patients have very retarded motor milestones and are hypotonic. They show unsteadiness, inco-ordination of voluntary movement and intention tremor They walk flat footed with their legs wide apart. Patients with "ataxic diplegia" are hypotonic in early infancy but later show spastic paresis more severe in the lower limbs than the upper in addition to the signs of ataxia. (They walk on their toes with greater or lesser degrees of adductor spasm.) A proportion are epileptic.

The clinical findings in a series of 60 patients with congenital ataxia seen in two Edinburgh clinics are reviewed. It is suggested that developmental malformations may be of greater aetiological importance than birth injury in both "ataxia and ataxic diplegia The course and clinical findings of both types of ataxic cerebral palsy are described and compared.

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Department of Child Life and Health
17 Hatton Place
Edinburgh 9
Scotland

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PROCEEDINGS OF PEDIATRIC SOCIETIES

Danish Paediatric Society

Meeting, September 14 1960

K Willen Jensen The Value of Some Methods of Investigation in th Study of Allergy

After a brief review of the limits of the value of the results obtained from cutaneous tests, eosinophil cell count in blood and secretions and Vaughan leucopenic index, the thrombocytopenic index elaborated by Storck *et al.* which is stated to be specific for allergy to foodstuffs and drugs, was reviewed. The method was tested on a series of hildren but such frequent discrepancies between the thrombocyte count and the clinical result of provocation occurred that the method ppeared to be particularly unreliable. Similarly cutaneous testing with group allergens, as opposed to individual allergens, was discussed and it was demonstrated that, employing the prick method, positive reactions to group allergens were obtained, particularly where foodstuffs were concerned, when the individual reactions were negative. Conversely with inhalation allergens, negative group reactions were frequently obtained, although one or more of the individual allergens gave positive reactions. Out f approximately 300 patients included in this investigation, discrepancies occurred in a total of 97

Discussion *J Vesterdal.* Is it possible that the discrepancy between the tests can be due to the fact that the foreign products contain extracts of plants, fish, etc. which are not present in Denmark? — *J Oster* The negative thrombocyt tests may possibly be due to the time factor A blood reaction is always somewhat delayed. — *P W Brandrup* Doubted whether the microthrombocyte count was so accurate that variations of 10% could be recorded. — *K. Willen-Jensen* There are no differences between the foreign and the Danish allergen test substances. Thrombocyt counts were carried out at ½ 1 1½ 2 hours after the test and in isolated cases as long as 6–7 hours after the test without any fall, even of 10%, being demonstrated.

O Steinicke A Case of Reticulosarcomatosis

Reticulosarcomatosis is a rare condition, particularly in childhood The condition frequently runs a prolonged but always fatal course. Th symptoms are very variable and uncharacteristic but are dominated by enlargement f peripheral or mediastinal lymph glands. The diagnosis can only be established histologically Radiation therapy may cause temporary improvement. In the Paediatric Department in Sundby Hospital, a case of reticulosarcomatosis was diagnosed in a boy in whom frequent, brief episodes of pyrexia had occurred since the age of nine years. These were associated with diffuse muscular pain and occasionally muscular infiltration without deterioration in the general condition. The boy became partially free of symptoms following prolonged steroid therapy Over five years later rapid enlargement of the cervical and mediastinal lymph gland occurred together with hepato- and splenomegaly Histological examination

of a lymph gland was then undertaken and revealed reticulosarcomatosis. Despite radiation therapy the boy died at the age of 14 years, a few weeks after the increase in growth of the lymph glands. The diagnosis was confirmed at autopsy. Until the final phase of the disease only lymphocytosis was demonstrated on repeated examinations and it is surprising that apart from isolated episodes with slight cervical adenitis, genuine enlargement of the peripheral lymph glands was not demonstrated until the final phase. The prolonged steroid therapy for nearly three years was possibly a contributory reason for this.

DISCUSSION: *Carl Friderichsen*: The first symptoms are suggestive of trichinosis. — *Torben Iversen*: There are many borderline forms both of malignant and benign conditions. In a series of 633 cases of leukaemia and leukaemia-like conditions, I found only six cases of reticulosarcomatosis.

Folke Tudvad: Prophylactic Vitamin D Administration in Premature Infants

In 63 premature infants (b. w. 950–2500 g) all of whom had received eight drops of Adetamin Fortiores (1600 I.U. vitamin D and 8000 I.U. vitamin A) from the age of 14 days, determinations of serum calcium, phosphate and alkaline phosphatase were undertaken at the age of 4–106 days. Only 22 (35%) of these infants showed neither lowered calcium, lowered phosphate nor raised phosphatase while 5 had lowered serum calcium (less than 4.3 mEq/l), three had lowered serum phosphate (less than 3.0 mEq/l) and 34 had raised phosphatase (over 35 King–Armstrong units). In addition, 24 had raised serum phosphate (over 4.2 mEq/l) probably as a result of feeding with cows'-milk preparations. The investigation suggest that the dose of vitamin D employed was too low. Attention is drawn to the relatively large dosage of vitamin A.

DISCUSSION: *P. W. Braestrup*: It has been demonstrated that increase of the dosage of vitamin D retards the growth in length. I consider therefore that the maximum prophylactic dosage of vitamin D should not exceed 800 I.U. even in premature infants. — *J. Flamand Christensen*: I do not employ dosages of more than 800 I.U. prophylactically for premature infants. Similar investigations to Dr. Tudvad but with this lower dosage are desirable. — *F. Tudvad*: When 65% of the infants in the material investigated have in fact blood chemical conditions as in rickets, I consider reduction of the dosage of vitamin D to be problematic. Nor do I consider that rapid growth or greater increase in weight can be used as the criteria of whether the correct treatment is being administered.

F. Tudvad, Copenhagen

Meeting September 28, 1960

Reginald Lightwood: The Home Care of Sick Children

Meeting October 14, 1960

K. Aagaard: Demonstration of a Boy aged Two Years suffering from Progressive Myositis Ossificans

Ossification commenced in the nuchal musculature and has gradually invaded greater parts of the musculature and impedes mobility to an increasing extent. As is frequently observed in this disease the thumbs and great toes are short and, in addition, hallux valgus and hypospadias are present. The patient is being treated at present with an acidosing diet as described by Frölich.

DISCUSSION: *C. Friderichsen* described how Frölich discovered the acidosis-produc-

ing diet during his studies on diabetes. — *P Plum*: What is the difference between this condition and dermatomyositis? — *K Aagaard* In myositis ossificans, the changes occur symmetrically and are associated with congenital deformities.

P Plum Spastic Paraplegia with particular Reference to the Aetiology and Course

To be published in *Acta Paediatrica*

P Plum and I Thern The Drug Treatment f Cerebral Paresis

The various drugs which have been submitted to trial in cerebral palsy during the past ten years were briefly reviewed With the exceptions of Mysoline and Librium, the results were unsatisfactory The desired effect was decrease in muscular hypertonicity and in the hyperkinetic movements. The effect of Librium was reported in more detail. Thirty patient were treated for one or more months and of these the 22 patient with extrapyramidal lesions responded definit ly better than th eight spastic children. The results were independent of the degree of severity of the disease, age and the intelligence of the children. There was great variability in tolerance to the drug The dosage employed varied from 2.5–30 mg daily The major side-effect was drowsiness. Drug therapy should be regarded as a supplement to other forms of treatment.

J Melchior The Prognostic Value f Pneumoencephalography in Childhood

The results of a follow up investigation of 271 children (171 boys and 100 girls), all of whom had been admitted t the Department of Neurosurgery Rigshospitalet during th years 1936–1955, and in all of whom suspected or definit dilatation of the ventricular system was found on pneumoencephalography As the method of measurement a modification of one of the ratios given by Evans (1942) was employed: greatest width of the anterior cornuae/greatest internal width of the cranium. It is emphasized that it must be correct to employ a relative figure in these patients who were frequently very young (over 50% of the patients examined were under two years) It was demonstrated that the prognosis was increasingly poor when the ratio was greater i e, with increasing degrees of dilatation of the ventricular system. Further it may be recorded that the width of the third ventricle is a very valuable measurement also in children and that the presence of increased quantities of cortical air indicates a poor prognosis. The reliability of the PEG findings is supported by examples from a series of patients in whom repeated PEG examinations were undertaken and compared with the pathological findings.

DISCUSSION: *Sv Brandt* recorded that a previous article by Erna Christensen, J Vesterdal & Sv Brandt, which was concerned particularly with surface air was supported, *inter alia* by Zellweger's findings concerning the instability of surface air in young age groups. Asked what the prognosis is in children with dilated ventricles, as he has seen a number of cases in whom good recovery occurred. In many of these cases, the circumference of the head was increased. — *J Melchior* The first question cannot be answered from the present material as it was selected in respect of dilatation of the ventricles. It is confirmed that increased circumference of the head frequently gives better prognosi as compared with subnormal circumference of the head which is practically always associated with a poor prognosis. — *J Vesterdal* reported that his previous investigation in 1953 did not show any good correlation between the clinical findings and the PEG picture. Markedly oligophrenic children could have normal PEG findings. Does cortical trophy render the prognosis worse? — *J Melchior* Yes. — *H Andersen* Is the investigation associated with any risk? — *J Melchior* A certain risk is present and two deaths occurred in the present material. On the other hand, however the

risk is not so great as t prohibit the investigation in the cases in which it is indicated. — *J Vesterdal* Can PEG be undertaken in very small children? — *J Melchior* There is no pparent increase in the danger in the young age groups and it is frequently in these age groups that the investigation appears t be most indicated.

Meeting, November 9 1960

P Plum: Reflex Dystrophy? Demonstration

H Andersen: Infantilism in Girls. Demonstration

A girl aged 15½ years with retarded growth and delayed puberty was demonstrated. A noteworthy feature was the very high protein content in the spinal fluid which was 450–374 mg%. Other investigations of the central nervous system, including PEG did not reveal any abnormality N explanation of the raised protein in the cerebro-spinal fluid has as yet been found. The history did not give any evidence of infections of any sort and suspected lead poisoning was disproved by examination of the urine. Hypothyroidism, dysgenesis of the gonads, etc. could be excluded. The patient has been discharged for continued observation. In connection with the demonstration, a brief review of the causes of infantilism in girls was given.

K. Aagaard: Haemolytic Anaemia. Demonstration

A case of congenital non-spherocytic haemolytic anaemia occurring in boy aged three years was demonstrated. Exchange transfusion had been carried out on the third day of life on account of increasing jaundice and splenectomy and prednisolone therapy had been instituted following a severe haemolytic crisis with haemoglobinuria during the second year of life. At present, without treatment, the patient has haemoglobin level of about 70%, reticulocyt count of about 90% and the serum bilirubin is bout 2 mg%. The diagnosis was established by exclusion (no evidence of acquired conditions, no abnormalities of the erythrocytes or haemoglobin, only 3 1% alkali resistant haemoglobin, no response to splenectomy) The parents, who were not related, do not show any signs of latent haemolytic disease

P Kildeberg A Case of Aldrich Syndrome

Following a brief review of our present knowledge of Aldrich syndrome a description was given of patient from the Paediatric Department in Odense suffering from this singular condition. The clinical picture with chronic eczema, thrombocytopenic haemorrhages and recurrent pyogenic infections, together with the almost complet absence of natural isoagglutinin in the patient serum, corresponds accurately t descriptions by other authors. As in many of the cases in the literature it was not possible to demonstrat the recessive sex-linked inheritance demonstrated by Aldrich *et al.* in this patient. No members of the patient's family appeared to have had the disease. The possibility of a congenital defect in the immunoglobulin met bolism is discussed and the striking genetic, clinical and serological points of similarity between Aldrich s syndrome and certain congenital immune pareses are emphasized. Analyses of the serum protein in this patient including immune electrophoresis, revealed generalized hyper immunoglobulinaemia, various abnormalities in the gamma-globulin fraction and an increase in the three specific alpha$_2$-globulins. The genetic serum type was found to be Gm (a-).

DISCUSSION *G Englesen* had seen a similar case in Lund in a girl aged five years of Danish origin. — *P Plum* has t present

two patients in the department who greatly resemble the case described. — *Friis Hansen* Were investigations for fractionated serum lipoids undertaken in view of essential hyperlipaemia? — *P Kildeberg* No.

Annual Meeting with Ladies, December 6 1960 in Domus Medica

Helger Poulsen Animal Babies

Meeting, February 8 1961

V Knudsen Successful Operative Treatment of a Tubercul ma in the Posterior Cranial Fossa

An Eskimo boy from Greenland, aged four years, was admitted to the Department of Neurosurgery Rigshospitalet in poor general condition and with stasis of the papillae, dehiscence of the cranial sutures and cerebellar deficiency symptoms, and was submitted to operation for a tuberculoma in the left cerebellar hemisphere. Postoperatively chemotherapy with streptomycin, PAS and isoniazide was administered. Six months after operation, the boy was healthy and free from symptoms. The 18 cases of tuberculoma admitted to the Department of Neurosurgery Rigshospitalet, during the past 25 years were reviewed and it was shown that the prognosis, which was previously hopeless, is now good as the result of the introduction of chemotherapy The disease is very rare in Denmark as, during the past 12 years, only three patients with tuberculomata have been admitted and two of these were natives of Greenland.

Discussion *B Friis-Hansen*. Was the patient Calmette-vaccinated and what is the prognosis? — *V Knudsen* The patient had not been Calmette-vaccinated. The prognosis must be considered to be good.

J H Probst The Preliminary Results of the Treatment of Muscular Dystrophy with Decadurabolin

The preliminary results of combined Durabolin–Decadurabolin therapy in four boys suffering from progressive muscular dystrophy are summarized In two of the cases, the therapy resulted in definite clinical improvement, while the other two patients were not influenced. The significance of reduction in the excretion of creatine and alteration of the creatine–creatinine ratio is emphasized. The fractionated 17 ketosteroids were traced and an increase particularly in the A-fraction, was demonstrated. In contrast to the falling creatine excretion, the SGOT SGPT and aldolase showed increasing values. No satisfactory explanation of this observation can be given. Virilizing occurred in all four boys. This was moderate and is regarded as a necessary evil for the results obtained. It is concluded that more extensive material is desirable which should also include girls and conditions such as the Werdnig Hoffmann paralysis, polymyositis, myotonia etc.

Discussion *J Vesterdal* mentioned the danger of premature closure of the epiphyses. — *P Plum* stressed that the picture of muscular dystrophy required investigation on several points. Perhaps the varying reactions to Decadurabolin therapy etc. may be of diagnostic value — *G Engleson* asked whether chromosome investigations have given information of diagnostic value — *J Schultz Larsen* Not t date. — *H Andersen* warned against the expression 'non virilizing anabolic steroid Hitherto the differentiation between these two properties has not been demonstrated with certainty in man for any of the compounds available. Our patient show definite virilizing with the dosages which result in im-

provement in muscular power in some of them. Muscular dystrophy is, however such a severe disease and hitbert a disease so inaccessible to treatment that it seems per missible to tolerate certain and probably reversible virilization and also a somewhat premature closure of the epiphyses as side-effects.

P E. Jensen Intolerance of Cane Sugar as a Sequel of an Enzyme Deficiency

A boy aged three months was admitted t the Department of Paediatrics, Odense Town and County Hospital. The infant had developed diarrhoea and loss of weight on changing from breast t bottle feeding The cause proved to be intolerance t cane sugar Tolerance tests with mono- and disaccharides and investigations of the urine and stools showed: (1) Defective hydrolysis of cane sugar in the intestine (no rise in blood sugar following ingestion of cane sugar although resorption of glucose and fructose was normal) (2) Increased resorption of unhydrolysed cane sugar while on an ordinary sugar containing diet and increased excretion of cane sugar in the urine (100 mg%), (3) The greater part of the cane sugar administered was excreted in the faeces, (4) Following administration of supplementary doses of the canesugar-hydrolysing enzyme invertase, conditions in the blood, urine and faeces were normalized and (5) The patient became symptom-free and thrived normally on a diet free from cane sugar Lactose and maltose were hydrolyzed normally in the patient's intestine and no evidence was found of other enzyme defects in the digestive juices. Isolated cases of diarrhoea due to deficiency of invertase maltase or lactase in the in testine have been reported in the literature. The occurrence of cane sugar in the urine of normal children has been described following tolerance tests, during severe gastroenteritis and in connection with hiatus hernia and oligophrenia. The linical picture in the patient described here is explained as a congenital enzyme defect in the intestinal juices, probably with complet bsence of saccha rase (invertase) which implies that cane sugar cannot be hydrolysed and, while a limited quantity is resorbed unhydrolyzed, the remainder is left in the alimentary canal where it exerts a laxative effect

DISCUSSION *S Brandt* Was the child mentally retarded? — *J Schultz Larsen* Were there any similar cases in the family? — *P E Jensen* The answers to both questions are "N " — *O Mortensen* reported that a boy aged eight years with intolerance of disaccharides had been studied in the Department of Paediatrics, Aarhus Municipal Hospital.

Meeting March 15 1961

H Kreutzfeldt: A Case of Death by Suffocation

A case of death by suffocation in an ordinary hospital cot is reported. A boy aged 2½ years wa found dead with his legs and body hanging outside the cot and his head jammed between the bars of the cot Several causes of death were probably involved as the child had a large papilloma of the larynx which filled the laryngeal cavity almost completely The author discussed whether the construction of hospital cots should be altered in view of this episode

B Zachau-Christiansen Death due to Suffocation in the First Years of Lif with par ticular Reference to Strangulation by Restraining Harnesses

Published in *Ugeskrift for Læger* 1961 123 1049

DISCUSSION *J Jensen* quoted case where a hild aged 1½ years fell out between the spaces between the bars of a cot The child hung by the head and died almost immediately The cause of death was shock on account of pressure on the larynx. The

space between the bars was 17.5 cm. Dr Jensen considered that accidents in small children are so varied that no typical accidents exist against which precautions can be taken. Dr Jensen did not consider that one type of harness can be recommended more than another — *H Friderichsen suggested* that a questionnaire from the Ministry of Health be sent t the matrons of all children s wards, children s homes, day homes and nursery schools and to health visitors asking how frequently they had seen accidents si milar to that described by Dr Kreutzf ldt (but not fatal) As it would be a big unde taking to alter all of the cots, such an in vestigation would perhaps be reasonable. — *K Biering-Sorensen* reported that already several years ago, health visitors had been very perturbed about the 'Star Harness on account of observations similar t that of Dr Zachau-Christiansen s, where children manged to become dangerously tangled up in the harness. Asked what construction could be recommended in cases where some harness is necessary e.g in prams. — *P Plum* If the connecting straps between the actual body harness and the mattress were so low down at the back that they only needed to be a few centimetres in length, accidents would probably be prevented. — *B Zachau-Christiansen* considered that there must be numerous accidents with the 'Star Harness" which have had a fortunate outcome when, in a few years, three serious accidents had occurred, two of which were fatal. Dr Zachau Christiansen had asked the manufacturer to discontinue advertising the harness as without danger For prams, Dr Zachau-Christiansen again recommended the Norwegian sheet-harness "Trygg"

Consideration of the Research Questionnaire sent by th Danish Medical Society

Following a discussion in which *J Vester dal, P Plum, E Fog B Friis-H sen, H Andersen, Sv. Brandt* and *F Tudvad* participated, a committee of nine was elected to elaborate the reply by the Danish Paediatric Society to the questionnaire from the Danish Medical Society

Meeting, April 12, 1961

Members of the Danish Surgical Society and the Danish Radiographic Society were invited

I J Carré (Belfast) Partial Thoracic Stomach

T be published in *Ugeskrift for Læger*

Discussio *Gr Thomsen* criticized the term "partial thoracic stomach The stomach had never been down in the bdomen. The diagnosis must be established by in vestigation of regurgitation. Mucous membrane folds passing from the stomach to the oesophagus are of value. Why do hildren develop strictures? — *I J Carré*. believes this to be due to the short oesophagus. — *P Plum* was surprized at the similarity between pyloric stenosi and hiatus hernia. — *J Vesterdal* What happens t these cases in later life? — *H Husfeldt* The surgical material is too limited. H had operated upon two children for pyloric stenosis where hiatus hernia was present. — *Chr H ssel.* Had these children small regurgitations? — *I J Carré* — No The somatic and mental development is not affected by treatment.

Meeting, May 17 1961

E. Rysang Ectop c Kidney

The case of a boy aged 4½ months with ectopic, malrotated kidneys was described. The renal pelves were slightly dilated, but th calyces were normal. There was no pyuria, the blood urea was normal and the

infant was thriving. There was a tendency to considerable regurgitation, probably on account of aerophagy. The development of the metanephron and its ascent were roughly outlined.

E. Brading: A Patient with Omphalocele and Diaphragmatic Hernia of Morgagni' Type

The next patient was a girl aged five month from Iceland. The infant had been submitted to operation on the second day of lif on account of a fairly large omphalocele. She was now admitted on account of cardiac symptoms, large cardiac shadow on radiography and failure to thrive. There were no cardiac murmurs and angiocardiography revealed that the heart was dislocated by a space-occupying process behind the sternum. Thoracotomy revealed a diaphragmatic hernia containing liver. The development of the omphalocele and the diaphragmatic defect can be placed chronologically about the 7th–8th weeks of foetal lif

B. Friis-Hansen: Unilateral Cystic Kidney

During recent years a total number of 36 cases of this disease have been reported. It is usually found in infants, where the first symptom is enlargement of the abdomen; but in contrast to the infantile form of polycystic kidney disease which is bilateral and f tal the multicystic disease is unilateral and can be cured by removal of the diseased kidney. A five-month-old girl was admitted to Dronning Louises Børnehospital with signs of a tumor in the right side of the bdomen. This had remained almost unchanged since it was first detected, when she was one month of age. An orange-sized kidney was removed, which consisted of unequal cysts, mostly of grape size with only a small lump of rudimentary kidney tissue found t one end of the tumour. At follow-up 2 months later the patient was well, with no sign of abnormality of the remaining kidney.

Sv. Brandt: The Aetiology and Pathogenesis of Acute Infantile Hemiplegia

Acute hemiplegia is rare in children but may occur as a sequel of haemorrhages from congenital vascular deformities in the brain or as sequelae of post traumatic oedema or arterial thrombosis of unknown pathogenesis. Congenital cardiac disease (cerebral embolism) and tumours should also be considered, particularly in older hildren. During the first 2–3 years of life and particularly in the first year of life acut hemiplegia occurs more frequently than in older hildren. The cause of these early pareses, which are always preceded by prolonged coma with repeated generalised or unilateral seizures, has always been obscure. Post traumatic oedema, encephalitis and occlusion f the arteries or veins, the latter being most frequently cortical, are among the suspected causes but frequently the causes are uncertain and in a number of patients difficult to prove. During a three-day meeting in Clevedon, Somerset, England, arranged by the National Spastic Society the conclusion was reached, after thorough discussions, that these infantile hemiplegias must to great extent, be regarded as post-epileptic in other words, as permanent post-epileptic pareses, although in many infant they had appeared in connection with the first manifestation of hitherto latent epilepsy. It is considered that the epilepsy is sequel of perinatal brain injury more frequently than was previously presumed. This assumption is supported by two observations (1) that a number of these children had experienced one or more previous seizures without hemiparesis and ( ) that air encephalography recorded as early as a few days after the acute paresis shows definit trophy of a hemisphere which must, therefore, ha been present prior to the ttack. Treatment, or rather prophylaxis, must therefore be more intensive treatment of epilepsy and be directed particularly against status epilepticus. Although the prolonged st tus epilepticus and the resulting anoxia of the brain produces unilateral symptoms in these chil-

dren, it must be presumed that the damage is, in fact bilateral more frequently than the hemiplegia *per se* would lead one to suppose. Follow up investigation of 25 patients with acute infantile hemiplegia which developed prior to the age of two years showed that many more of these had subnormal intelligence than patients with congenital spastic hemiplegia had. At the conference in Cleveton, other possibilities of abbreviating the damaging influence of the ischaemic oedema were discussed: the injection of hypertonic solutions of urea and cooling of the patient. On the other hand, there do not appear to be adequate reasons for institution of anticoagulation therapy except perhaps in those cases where it is considered certain that the acute hemiplegia is of embolic vascular nature Further the significance of maintaining the possibilities of adequate collateral circulation in the brain by preventing shock with fall in blood pressure were emphasized.

DISCUSSION: *F Quaade*. In the Department for Infectious Diseases, Blegdamshospitalet, we only rarely see the clinical picture described by Dr Brandt, although we have seen a great number of children with seizures of other aetiologies, most frequently febrile. From the past 2½ years, I remember two children with hemiparesis following violent attacks of coughing in whooping cough (probably caused by cerebral haemorrhage rather than by the somewhat doubtful "whooping cough encephalitis) and two which developed as complications of tuberculous meningitis. Were any of the idiopathic cases in children which Dr Brandt mentioned already recognized as epileptics? It seems reasonable to presume that the seizures *per se*, irrespective of the cause, are the dominating pathological factor as they are frequently associated with cessation of respiration or at any rate, hypoventilation with anoxia of the brain. As prophylaxis against the neurological sequelae described, the following measures should be taken. (1) eliminate the seizures rapidly (adequate doses of barbiturates; curare if necessary) and (2) simultaneously ensure adequate ventilation (frequently and in curarized patients, of course, always mechanically) and in this way oxygenization of the blood — *H Dygge* asked what the prognosis is for children with febrile seizures and transient hemiplegia. What are the chances of recurrence with renewed febrile seizures? Is there any risk of permanent hemiplegia? — *K Wilken-Jensen* In the comprehensive and instructive review I thought an isolated item was not mentioned and I should, therefore, like to ask whether the possibility of allergy should not be considered in connection with the oedematous changes in the brain. According to an English work, 10% of all epileptic clinical states are allergic in nature so that the symptoms disappear on elimination of the allergen from the diet and Professor Susan Dees from Duke Hospital, Durham, has, as far as I can remember also described EEG changes as sequelae of allergy In Rigshospitalet, some time ago, we saw an infant with increasing symptoms of oedema of the brain. The symptoms disappeared when breast milk was administered. Provocation tests were not undertaken on account of the risk involved and the infant was discharged in good health.

C. J I gemar & E. Tersler Postoperative Hypertension as a Complication of Resection of Coarctation of the Aorta

An account was given of the course of the blood pressure postoperatively in 33 children, aged 2 months to 13 years, who had been submitted to operation for coarctation of the aorta in the Paediatric Department, Rigshospitalet, and in Queen Louise Hospital for Children during the period 1950–1960 Five of the children, i.e. 15%, developed reactive hypertension. In one of these patients, the reactive hypertension was presumably of renal origin as, in the postoperative period, anuria also developed and at autopsy a recent renal infarct was demonstrated. In two of the other patients, certain urinary symptoms in the postoperative period also suggest the same reason, as

polyuria with haematuria occurred in one patient and albuminuria (with gangrene of the intestine) in the other Two out of the five patients died. The most important aetiological factor in reactiv hypertension was considered t be injury in the regions of organs, where there had been hypotension preoperatively caused by the sudden increase of blood pressure which occurred after resection of the coarctation and, as prophylaxis, it is suggested that the clamps on the aorta should be opened very slowly after resection.

H Andersen Copenhagen

The Pediatric Society of Southern Sweden

Meeting April 16, 1961

S. Refstedt Treatment of celia disease with unsaturated fatty acids

By fat-balance studies it could be shown that in children with celiac disease the resorption of unsaturated fatty acids is better than that of saturated. On the basis of these findings a gluten-free corn oil diet has been worked out adaptable t different age groups. During the last 2 years 3 children with celiac disease have been admitted to the hospital in an emaciated condition at the age of 6–12 months. After treatment for 2–3 weeks the stools became normal; in connection with this the f t resorption improved towards normal values, usually around 80% compared with 40% prior to the treatment The hospital treatment lasted for 3–6 months, and the patients were not discharged until they were in very good condition in all respects. The mothers have been carefully instructed in regard t the diet and have continued this t home. When growth, general condition and stools had been normal for some time bread and gradually also animal fat were added. Occasionally in this connection the stools became more watery and voluminous, but by slow adaptation in 2 cases the diet could gradually be changed to completely normal food. In one case the mother had t be caref l with bread, but on the other hand, animal fat in moderat amounts was tolerated by this patient These cases indicat that if celiac patients are kept on a gluten free corn-oil diet for a sufficiently long period the atrophic intestinal villi will have time to undergo restitution and thereby a normal tolerance of food can be restored.

G Malmström: Three cases f osteitis

During recent years an increased frequency of osteitis cases has been observed in different countries. Usually these have been of bortive type probably due to the fact that they were detected in an early stage and subjected to adequat therapy In many cases the osteitis has been an isolated phenomenon, without signs of another infection. In one of the 3 cases the infection was localized in the patella The bone destruction was discovered first after repeated roentgen examinations. In spit of i tensive antibiotic therapy sequestration took place, which, however was healed without sequelae with an insignificant bone defect In the second case the osteitis wa localized in the distal part of the right tibia. Also in thi case there was a slight sequestration, which, however was healed with prolonged ant biotic therapy In the third case the bone destruction was localized mainly in the cuboid bone There was no sequestration in this case, only a serious decalcification The therapy in this case was also ant biotics over a long period with complet return t health.

Meeting, October 23 1961

G Edgren Gonadal dysgenesia (Turner's syndrome)

Markedly undersized 14-year-old girl with signs of sexual infantilism. No symptoms of pterygium. Hormone analysis of the urine showed increased excretion of gonadotropin and decreased excretion of estrogens. Cytologic examination of the epithelial tissue f the mouth was chromatin-negative. The girl has 45 chromosomes with a XO state. Hormone therapy with estrogenic hormone for periods of 3 weeks with an interval of 1 week, combined with corpus luteum hormone during the last of the 3 weeks has caused a striking development of secondary sexual characteristics, a regular menstruation-like bleeding and, apparently stimulating effect on the growth in stature

G Edgren. Ehlers–Danlos syndrome

A 6 year-old girl exhibited extreme elasticity of the skin, hyperlaxity of the joints and fragility of the skin and blood vessels. The blood picture and coagulation conditions were normal. There were some cutaneous bleedings and several thin scars as well as so-called pseudotumors, particularly in the regions subjected to trauma. There was no known heredity for the disease

Swedish Pediatric Society

Meeting March 11 1961

Panel Discussion on Immunisations in Infants and Small Children

B Malmgren Pertussis vaccination

In 1931 Leslie & Gardner observed the appearance of phase changes in the organism causing whooping cough, *Bordetella pertussis* Since then, the attempts to produce specific protection against whooping cough have been on firmer footing The English field trials, mad under the sponsorship of the Medical Research Council during the 1950's, gave final proof of pertussis vaccine s effectiveness. Pertussis bacteria produce several antigenic systemic and biologically active factors of which some can be labeled as endotoxins. It is thus possible t demonstrate in animals, the neurotoxic effect, the skin necrotizing action, a histamine sensitizing property and evidence of the occurrence of pyrogenic substances. According to animal experiments, none f these toxins is thought t be essential for the development of immunity against *B pertussis* It is possible that one or more of these substances may be responsible or may contribute t the development of these complications following vaccination f children. Thus attempts should be made to develop product which contains the antigens but which is free of the toxic factors. The results of experiments conducted at the Bacteriological Department of Karolinska Institutet show that an atoxic substance composed of bacterial cell walls protects experimental animals from lethal doses of pertussis bacteria.

B Hellström Central nervous system reactions f llowing pertussis vaccination

The central nervous system reactions following pertussis or triple vaccination which are described in the literature have been of three different types. The most

benign reactions have consisted of short seizures without sequelae comparable to febrile convulsions. The second type has been characterized by a serious encephalitis-like picture with unconsciousness, prolonged seizures, a high incidence of persistent neurological defects and in some cases even a fatal outcome. In the third type, appearing as a more slowly progressive mental deterioration with or without convulsions and sometimes having the character of infantile spasms, the connection with the immunization often seems more doubtful. In Sweden, the problem of these complications has been of current interest since 1959 when J Ström reported several cases and calculated the risk of more severe reactions as 1 in 17 000. A committee organized by the Royal Board of Health re-evaluated the reported cases and estimated the risk as 1 in 50–60,000 cases. In order to investigate the incidence of possible subclinical cerebral reactions, EEG examinations have been performed in 84 infants in connection with triple vaccination before and at cert in intervals after the injection. In none of these cases were EEG changes attributable to the immunization observed. In five other infants who had shown more prolonged febrile reactions following a triple injection an EEG taken within a few days did not reveal any abnormal findings. It is planned to increase the series by including cases which showed more unusual general reactions following the vaccination. A neuropediatric evaluation of each case where a suspicion of cerebral reaction has been reported, is essential. In Sweden such complications following any immunization procedure must be *reported to the Royal Board of Health.*

B Melén: Combined vaccination against poliomyelitis tetanus, diphtheria and pertussis

The results of combined vaccination of infants against polio tetanus, diphtheria and pertussis are reported. One American and one Swedish vaccine were tested. The infants were given three injections of 1 ml each at 6-week intervals, starting at the age of 3 months. Pre and postvaccination blood specimens were examined for neutralizing poliomyelitis antibodies and agglutinating pertussis antibodies, as well as tetanus and diphtheria antitoxin. It was found that the response of the infants to the diphtheria and tetanus components of the vaccines was very good, while the results with the pertussis component were only fairly good. Detectable maternal antibodies to these antigens were observed in very few of the infants. The response of the infant to the poliomyelitis component was definitely poorer The majority of the infants had high titers of maternal antibodies and did not respond at all. Those with no detectable maternal antibodies or with antibodies of low titer however generally responded excellently The two vaccines tested did not differ significantly as to effectiveness. It is concluded that, in early infancy when vaccination against poliomyelitis is performed, either alone or in combination with other antigens, vaccines must be used which have a considerably higher antigenicity than those now in general use If such concentrated poliomyelitis vaccines are not available, vaccination should be postponed until the maternal antibodies have fallen to a low level.

S. Gard. Live poliovirus vaccine

The Swedish experience of inactivated poliovirus vaccine has been excellent. Nevertheless there are two reasons for use of live virus vaccine as a complement to the inactivated. (a) Type 1 is the weakest component of the inactivated vaccine It would seem advisable to look for a method by which higher serum antibody titers could be attained and, presumably longer duration of immunity (b) Since exposure to live virus evokes intestinal resistance to reinfection, sufficiently extensive use of live vaccine would tend to restrict circulation of wild virus, thus providing, indirectly a certain protection also of non-vaccinated persons.

A strain of virus to be used as a live vaccine should fulfill the following requirements.

A. *Non pathogenicity to man* Only large-scale field trials—involving 100 000 or more susceptible individuals—may provide information on this point; simultaneously circulating wild viruses may make evaluation difficult or impossible. Candidate strains for vaccines have been chosen on the basis of neurovirulence tests in monkeys; to what extent this character is correlated to human pathogenicity is unknown. Certain other "genetic" markers show a correlation to neurovirulence e.g capacity of growing at higher temperatures or at low bicarbonat concentrations. Dr Margareta Böttiger has found that certain strains grow better in human than in simian tissue, while the reverse is true of others. It would seem rational to choose vaccine strains of the last-mentioned character

B. *Restricted capacity of spread by contact infection* Since no poliovirus strains show complete genetic stability a tendency to spread with repeated human passages clearly poses a problem. Capacity of spread is proportional to infectivity Vaccine strains, therefore should possess only restricted infectivity on oral administration and should not be too well adapted to human tissue. Children aged 6 months to 3 years seem to spread infection more readily than older children who have learned personal cleanliness.

C. *Genetic stability* Changes in virulence are easily produced in the laboratory Such changes do also occur in vivo in the intestinal tract. Types 2 and 3 have proved notoriously unstable while fortunately Type 1 seems to possess a higher degree of stability

D *Good immunizing capacity* Generally speaking this is a matter of dosage; every "take" seems to produce a satisfactory immune response Infants less than 2 months, however show increased resistance to infection and their immune responses are weak.

E. *Absence of extraneous agents.* The risk of introduction of foreign agents from latently infected monkey kidney cells used for vaccine production has to be seriously considered. We try to eliminate such risks by inclusion in the culture media of pooled normal monkey serum that can be expected to contain antibodies to most common simian agents, and by treating the final product with monkey gamma globulin.

After due consideration of the difficulties in ascertaining the complete safety of any given vaccine strain we have decided not to administer live virus, unless a basic serologic immunity has first been established by at least two injections of inactivated vaccine; household contacts of prospective vaccines are also required to have their two shots. At present there seems to be no particular need for Types 2 and 3 live virus vaccines. According to the principles now adopted, an extensive immunization with inactivated vaccine of the whole population is a prerequisite for mass application of Type 1 live virus vaccine. Immunization of infants with live virus is not recommended. Instead the following schedule is recommended. 6 to 1 months three injections at monthly intervals of inactivated vaccine, suitably as polyvaccine (diphtheria, tetanus, polio), live Type 1 virus at the age of 2 to 3 years; live virus booster during the first school year

B Vahlquist Immunization programme for infants

It is essential to establish a standard immunization table This is particularly important for the first year of life, when it is desirable to carry out a large number of immunizations during a short period. The table must be flexible, so that changes can be made to fit in with changing patterns of disease and new achievements in the field. Poliomyelitis vaccination should now become part of the routine programme of the Child Welfare Centers to replace mass immunization campaigns. Three different programmes have been on trial in Uppsala since autumn 1959 and all of them include poliomyelitis immunization during the first year of life. On the basis of experience so far

Symptom	Time interval, hours 0–3	4–6	7–12	13–24	25–48	49–72	73–96	97–120	121–168
Convulsions	3	9	6	7	3	0	2	1	2
Coma	2	0	2	0	2	1	0	0	0
Shock	1	6	0	1	0	0	0	0	0

gained the following two alternatives are proposed. (1) *Under present circumstances.* *BCG* at birth, *triple vaccination* (diphtheria, tetanus, and pertussis), 3 injections during the period 3–6 months of age; *polio vaccination* 2 injections at 8 and 10 months of age, with a booster dose at 18 months; *smallpox vaccination*, on some occasion during the second six months of life. (2) *If a highly effective quadruple vaccine (polio diphtheria tetanus and pertussis) can be developed. BCG* at birth; *4-vaccine*, 3 injections during the period 3–6 months of age and a booster dose of *polio vaccine* at 18 months; *small pox vaccination* at some time between 6 and 12 months of age.

J. Ström: Cerebral and other reactions associated with triple inoculation

My article in the *British Medical Journal*, 1960 concerning cerebral reactions associated with triple inoculation, was followed by a comment by Malmgren, Vahlquist and Zetterström, published in the same journal. In this, mention was made of the committee appointed by the Medical Board to review my findings. This committee came to the conclusion that, of four deaths, three (two of shock and one of encephalopathy) must be accepted as having been caused by the inoculation. The fourth case also of encephalopathy was considered to be not entirely convincing. Furthermore a clear connection was found in a case of cerebral palsy associated with mental retardation and epilepsy. Moreover the injections were said to have a definitely provocative effect in cases of convulsions, coma, etc., but proof was considered lacking that subsequent symptoms were caused by inoculation rather than by other latent diseases. The material included in my earlier report covered the years 1955–1958. In 1959 a patient with convulsions for one week was seen. On lumbar puncture, nine cells were present. Another patient had fever for two or three days, and was drowsy for a week following the first injection. After the second injection, he had repeated convulsions of increasing severity and frequency one week later and subsequently developed cerebral atrophy. Lumbar puncture: seventeen cells. Toxoplasma reactions and W. R. negative. A third child had convulsions one week after the injection, and subsequently had hypsarrythmia on the EEG. One case of shock occurred. During 1960, 5 cases of convulsions were reported. One patient developed convulsions after a week, and was later found to have hypsarrythmia, as in the 1959 case. Shock occurred in 4 cases. I have made a summary of the major acute symptoms, and the time interval before the reaction occurred, where this could be ascertained. This material includes 33 cases of convulsions, 7 of coma, and 8 of shock.

Only convulsions of a general nature were included. Tonic convulsions were also reported sometimes. Fever was probably very often present but the temperature was not always taken or reported. Seven of the 8 shock cases occurred within 6 hours, and one after 20 minutes. Two continued until death. During the years 1953–1960 a total of 34 cases were treated at hospitals for an inoculation reaction, and a further 48 cases of greater interest were observed in out-patient departments. Pathogenically the reaction was probably of toxic, allergic or mixed type. Sometimes the condition was associated with urticaria, edema, and erythema, and suggests an allergic component. As regards the subsequent course an autoimmunogenic process precipitated by primary toxic damage to nerve tissue may be involved.

DISCUSSION *Vahlquist.* It is noteworthy that Ström still cites completely unsifted material obtained by investigation among the country physicians. With my coworker Bronson, I have had an opportunity to examine carefully the reported material on "triple complications occurring in 1959 As might have been expected, loser examina tion in many cases shows that proof of a real causal ffect of central nervous system in jury by vaccination is very weak. Of 25 cases reported in the given year many can be immediately excluded, for instance, because the reported vaccination was not carried ut during the current year or because it was a case of osteoarthritis, not a central nervous system injury etc The two cases specially cited by Ström which subsequently developed cerebral atrophy namely hypsarrythmia, showed central ner vous system symptoms in the form f con vulsions before vaccination. It is clear that with such uncritical handling of research data almost any desired result can be arrived at. Our closer examination of the above-mentioned 25 "triple complications from the year 1959 showed that an indication of persisting central nervous system injury was present only in the 2 already mentioned cases, both f which before vaccination ex hibited convulsions. A further report on the result of our investigation will be published in *Nord Med.* I will not go so far as to assert that serious complications can never arise from triple vaccination, but it is reasonable to ask that ordinary scientific objectivity be displayed in the process f analysis. — *R Lagercrantz.* There are many good reasons for vaccinating babies as early as possible. Protection against whooping cough is needed immediately and early smallpox vaccination, as E. Rabo has shown, is less troublesome than when carried out later Furthermore, injections at this age do not give rise to fear of doctors. It is also easier to organize an immunization program during this period, because health super vision at the children welfare center is particularly intensive. The number of in jections, however should not be too great. A program consisting of three injections of triple vaccine inoculation against smallpox and three injections of polio vaccine before the age of eighteen months is difficult to carry out. The pediatrician should demand access to an effective quadruple vaccine which can be administered during the first six months of life, that is, one whose polio vaccine content can effectively counteract the influence of maternal antibodies. That it is possible to produce such a vaccine is obvious from th experience reported to the Society last autumn by Professor Gaisford. It should also be remembered that Professor Gaisford strongly emphasized that vaccination against whooping cough should be continued, and that the advantages outweighed the disadvantages. As regards tetanus prophy laxis, we agree with Hans Ericsson and the surgeons on the desirability of a general active immunization, and that only broad scale triple vaccination of infants can guar antee such immunization. During 1959 and 1960, 94% of newly registered infants were triple vaccinated at Norrtull Child Welfare Center in Stockholm. This program did not adversely affect other activities, including our long-standing interest in problems of mental hygiene in which we have been assisted by a child psychologist During the past two years, 194 children received complete triple immunization, that is, three injections between the ages f two and six months. Thirty four children were vaccinated once or twice. In 16 cases, the series was not completed because of an unusually severe reaction, such as high fever of more than 1 hours duration and/or more pronounced general side-reactions. In no case were convulsions or lasting ill-effects observed after vaccination. Injections were administered deeply subcutaneously in alternating gluteal areas, and the injection site was briefly massaged. Local reactions were as a rule, insignificant or moderat After a total of 640 injections, five cases were noted of progressive local swelling which required incision and were followed by healing.

Meeting September * 1961 in Västervik

Masberg, H.-O. Social medicine conditions among in-patients in the Children's Ward, Centrallasarettet, Västervik, compared with a similar investigation carried out t Samariten Children's Hospital, Stockholm

The Samariten examination from 1956 showed how altered social circumstances during the decade from 1943/44 t 1953/54 were reflected in hospital data concerning children in a large city. A corresponding investigation in Västervik during 1957 59 showed how these social hanges penetrated t provincial towns and the surrounding countryside. The results showed that social changes affected even villages, though to a lesser extent than the metropolis. (Will be published in detail in *Social Med Tidskr*)

Hanström, E. and Masberg, H.-O. Eye examination of 2 year-olds from the Child Welfare Center

Of 250 available year-olds at Västervik Child Welfare Center 176 submitted voluntarily to an eye examination. Fundu scopic examinations were carried out. Skiascopy by Rosengren method without dilatating the pupil and without cycloplegia was carried out. Examination time was less than 6 minutes per child. Of 176 children, 2 refused t cooperat In 148 children, the findings were essentially normal, and refraction ared between ±0 and +1. Six children had defects other than those due to errors in refraction, tw had allergy one had blepharitis, one nictitatio, one a hori oidal scar of unknown etiology and one was suffering from the fter-effects of recent eyeball injury

Twenty children (11.5) had refraction defects (1) 3 hildren hypermetropy < dptr but 1 dpt ( ) 5 children hypermetropy 2 dptr.; (3) 8 children hypermetropy astigmatism; (4) 3 children one sided refraction defect; (5) 1 child suspected myopia, approx. 1 dpt Refraction was erified through skiascopy after tropine had been installed in their eyes for three days, as a result of which a ariation in the hypermetropy scale of about 1 dptr in relation t the primary value was obtained. The child with suspected myopia had HV + 0 75 dptr Glasses were prescribed for 11 f these *0 children (6.25 % of the total mat rial) All *0 children with errors of refraction were placed on a list for further examination at the Child Welfare Center t receive eye exercise tests as soon as possible Manifest strabismus was not encountered. The methods are simple and can with advantage be employed in the Child Welfare Centers. Obviously in a number of patients it sorts out the more glaring errors of refraction, in accordance with the findings of more extensive cycloplegical examinations of children (Skorsky)

On the basis f these findings, further study f routine ey examination in this ge group is recommended.

Jönsson, B. Cases from the Hospital records, 1956–1961

A series f 25 interesting and unusual cases were briefly described and presented with coloured slides.

Masberg, H.-O. Feeding f newborns in the infant ward

A study of timed demand breast feeding was carried out in the infant ward t Västervik Centrallasarett Half the infants were fed according to this principle and half according to the old system, with scheduled feeding. Demand feeding was found suitable for nearly all infants weighing more than 3000 g t birth. Additional feedings ere required for half the infants weighing less. The mothers total amount f breast milk wa obviously greater with demand feeding. The day for minimum weight of the babies and weight increase from minimum weight t weight at time of discharge was the same

in both groups. The maximal weight decrease was about 50 g more when the birth weight was over 3500 g, but in other cases the same. On discharge from the hospital, 82.7% of the babies on demand feeding and 36% of the infants on scheduled feeding were solely breast fed. The infants apparently suffered no adverse effects as regards general well-being and weight maintenance.

Meeting October 13 1961

B Hellström A Case of Congenital Analgia

Congenital analgia in children has not previously been described in Sweden. In a 2½ year-old, mentally normal girl, a generalized indifference to pain became obvious at three to five months of age when she received triple immunization. From five months onwards she began to vigorously suck and chew her fingers with resulting fissures which were easily infected. Subsequently burns, injections, incisions and other traumata have been tolerated without any reaction indicating pain. She has also been conspicuously indifferent to cold and has not reacted adequately on tickling or itching insect bites. Occasionally however abdominal pain has been a complaint No seizures or other attacks suggesting epilepsy have been observed. On examination she demonstrates a generalized indifference to potentially painful stimuli such as pricking or touching with sharp and hot objects. Other qualities of sensation could not be tested due to poor cooperation. Tendon reflexes were generally hypoactive, but no other reflex or motor abnormalities were found on neurological examination. An EEG demonstrated a marked, bilateral epileptogenic abnormality with continuous occurrence of bi and triphasic sharp waves both synchronously and asynchronously An X ray investigation of the hands and feet revealed dysplasia of some distal phalanges and signs of an osteitis in one finger This patient corresponds well to the picture described in the literature as congenital analgia, a condition so far reported in around fifty cases. In some of these a connection with epilepsy has been mentioned either among the patients themselves or among close relatives. EEG changes of the type and intensity present in this case have not been described previously This finding favours a central cause of the syndrome in contrast to the proposed pathogenesis of a sensory radicular neuropathy where atrophy and dysplasia of peripheral nerve endings or sensory nerves may be observed histopathologically probably secondary to degenerative changes of the dorsal root ganglia. Such changes have not been reported in congenital analgia.

B Ivemark & G. Wallgren Hamman-Rich's Syndrome in an Infant

Following a short review on the history frequency and clinical features of the disease a case report was given of a 2 month-old girl, who at the age of five weeks presented fully developed symptoms of interstitial pulmonary fibrosis with alveolo-capillary block Clinical physiological investigations revealed a markedly lowered diffusion capacity and an exceptionally depressed lung compliance amounting to only 20% of the predicted value The authors emphasize that the combination of these two signs of pulmonary impairment in the absence of underlying cardiac disease are seemingly specific for the disease The anatomical basis of pulmonary dysfunction was demonstrated by biopsy material from the case presented.

M Böttiger S. Gard & R. Lagercrantz Vaccination with Li Polio-virus — Facing Mass Vaccination

Th. Ehrenpreis, R. Lagercrantz & U Rudhe Regional Enteritis (Crohn Disease)

Regional enteritis has been considered uncommon in childhood but t Karolinska

Sjukhuset Paediatric Department eight cases have been diagnosed during the last two years. The main symptoms in these patients have been diarrhoeas, tiredness, mal nutrition, weight loss, abdominal pain, hypochromic anaemia, and high sedimenta tion rat In comparison with patients with chronic ulcerative colitis these patients have as rule been in worse general condition, with complaints of more fatigue and more pronounced abdominal pains, often with a palpable abdominal mass, and three f these cases presented anal fistulas. In contrast, they have had less bleeding and proctitis than ulcerative colitis patients. The ordinary resorption tests (Xylol and A vitamin and B balance test) have as a rule been normal even in malnourished patients. The differential diagnosis has been based hiefly on the roentgenological examination of the gut. In contrast to what might be expected the colonic manifestations of Crohn disease have dominated the roentgen picture in the eight cases encountered. The inflammatory processes have predominantly affected the right side of the colon but have also involved the descending colon and the sigmoid in some cases. Mucosal oedema, pseudopolyposis and extensive ulcerations, often with linear orient tion and segmental distribution, have characterized the lesions. Strong contrac tions, reduced capacity of the colon and thickening of its wall were also observed. Strictures were seen in some cases. Typical alterations of the ileum were found in 7 cases, in 5 of them in continuity with a imilar process in the colon and in one case complicated by a stenosis producing com plet obstruction. One patient with anal stricture and perirectal fistulas developed within one year an extensive inflammatory disease of the colon. The treatment has consisted of high calorie high protein diet with supplementary vitamins and iron, blood transfusions and spasmolytics All cases ha received Azulfidine (Salazopyrin) for long periods and five were treated with orally administered corticosteroids. The medical treatment has as a rule been beneficial symptomaticall but has not stopped the progression of the disease Four cases have been treated surgically The indications have been suspected appendicitis (1 case) marked stricture of ileum (1 case) and severe progressive disease during medical therapy (cases). At the operation an ttempt was made to resect all the diseased bowel. In two cases this meant a resection of the distal part of the ileum, caecum and ascending colon. In one case the terminal ileum and most of colon was resected. In the fourth case the disease was so widely spread that it was necessary to resect the terminal ileum, colon, and rectum and give the patient a permanent ileostomy Histologic findings were those usually seen in Crohn disease All patients withstood their surgery well and were discharged after an uncomplicated convalescence All patients improved con siderably both regarding their general con dition and local symptoms. However in three cases who have been followed for bout one year after operation there have already appeared clinical as well as roentgenological signs of new involvement in the ileum proximal t the resection.

DISCUSSION *B Sndlman* At St Görans Hospital, Stockholm, eight cases with inflammatory lesions in the lower bowel have been encountered which are of special interest Their clinical features and pathologic anatomy are strikingly similar and they seem to represent a special type of the disease which has not previously been described. The onset of symptoms was insidious with loose stools noticed for from one t several years, occasionally with blood and mucus. All patients developed perianal abscesses and fistulation. Examination initially showed proctitis with submucous granulomas and deep ulcerations in the rectum. The perianal fistulas present started from these ulcerations. Barium enema examination showed changes in the bowel, sometimes up through the sigmoid and occasionally extending up into the transverse colon. Biopsy from the rectal mucosa and lcerations showed granulomatous inflam-

mation with lymphoid infiltration and epi theloid changes. No tubercle bacilli were found and none of the patients had active pulmonary tuberculosis. The histological pic ture was identical with that of Crohn disease of the small bowel. In one case there was only fibrous tissue and no granu lomas. Apparently this case was investigated in the healing stage In four cases the disease was present also in the proximal colon. All patients developed fibrous strictures in the upper anal canal, rectum or sigmoid in the course of time One case healed with vigorous cortisone therapy The other cases had to be operated upon because of strictures, intractable fistules or malnutrition. The operations performed were partial or total colectomy with colostomy or ileostomy N pathological changes were observed in the small bowel This could be verified histologically by the operative specimen in three cases examined grossly during partial colectomy in three cases and observed by negative X ray examination in the two cases not perated upon. — *A Ekengren* Based on an experi ence of one hundred cases of regional enteritis, the absolute indications for surgery are proposed to be ileus, fistulas, palpable abdominal mass, severe bleeding and/or progressive deterioration. These symptoms, how ever represent late stages of the disease The main feature in the pathogenesis seems to be the progressive stenosing lymphangitis, which has been proved on operation by dye injection into the lymph vessels. Early radical operation with removal of the lymph vessels and lymph glands in the mesentery may halt the spread of the disease to other parts of the gut. Our results with such an operation have been encouraging Preoperative sterilisation of the gut with antibiotics for 24 to 48 hours seem to have improved the results and bortened the period of convalescence. Treatment with corticosteroids is beneficial symptomatically in some cases but only temporarily and in general such therapy is contra indicated. The patients must be under constant observation after operation. Signs of malabsorption of fat carbohydrate, protein and B vitamin must be looked for

R. Lagercrantz, Stockholm

BOOK REVIEWS

A C. Sørensen (Editor) et al. Human Genetics.

British Medical Bulletin, Vol. 17 No 3, September 1961 pp 177–264 Price 20 shillings.

This ymposium is composed of 15 chapters written by leading British uthorities and gives a comprehensive review of the field of human genetics of today One of the most interesting developments in this field in recent years has been the discovery of chromosome abnormalities in certain diseases. The five chapters devoted to clinical ytogenetics give a clearly detailed and comprehensive view of the current knowledge in this field. Other chapters of special interest to the pedi trician are those concerning galactosemia, aminoaciduria and pharmacogenetics. Although all of the chapters are well written, the reviewer wishes to call special attention t the last chapter which is concerned with the frequency of congenital and hereditary disease. It is a joy to read because of its clarity and style This volume is highly recommended for every linician interested in inherited diseases.

K H Gustavson Uppsala

Gerhard Lindemann Refraktometrie der Frauenmilch.

Gust v Fischer Verlag, Jena, 1961 DM 12.20.

Refractometric examination of milk serum, that is, the liquid remaining after protein and fat have been removed, has long been employed as a relatively simple method to detect adulteration such as the dilution of milk with water Refraction owes its occurrence t the presence of lactose. In cow milk, the salt play a special role. Clear milk serum is required for this method. Such serum is easily produced The proteins in human milk are, however signi ficantly more difficult to remove One can easily obtain weak opalescent serum. In this study several different methods of re moving protein are very carefully tested and Esbach reagent with kaolin added is recommended as the method of choice Technical details are exactly reproduced (page 20). The conclusions are based on analysis of more than 5000 tests. The author is able to demonstrate and this is important that there is no single refraction value for human milk, and no standard value can consequently be established. Refraction values therefore vary considerably t different stages of lactation, with a lower value occurring in the later stages. Girls under 20 years of age have for some unknown reason higher value. Considerable daily variation in refraction of milk serum from the same nursing mother occurs, due partly t such causes as the onset of menstruation, febrile illness and partly t unknown causes. Increased maternal carbohydrat consumption may also play a role. It also ppears that refraction of human milk has only limited value when it is a question of un masking the addition of water or cow milk in deliveries t the human milk bank However it would ppear that this method a developed by the author could be of value in commercial research.

Fell Nordbring Uppsala

Erik Thamdrup Precocious Sexual Devel opment.

A Cli ical Study | 100 Childre Munksgaard, Copenhagen, 1961 237 pp Dan. kroner 40- —

This investigation includes 100 patients from various hospitals, and constitutes a linical study of children with premature sexual development. The material has been divided int the following groups: true precocious puberty adrenogenital syndrome hormone-producing gonadal tumours, incomplet precocious puberty premature breast development as well as a hard-to-classify group of probably exogenic hormonal origin. The criterion for precocious puberty has been sexual development beginning before 8 years of age in girls and 9 years in boys. Very probably the material includes all known cases in Denmark during a parti cular period, which means that the annual incidence of precocious puberty is about 4 girls and 1 boy in a population of about 4,500,000

True precocious puberty Forty five girls and 11 boys come under this heading Of these 11 girls and 7 boys had cerebral da mage resulting from internal hydrocephalus hypothalamic tumour etc. Other cases are considered to have a purely constitutional disposition towards early sexual maturity This judgment is also supported by the early onset of menses in number of female relatives of these children.

Adrenogenital syndrome. Seventeen cases fell within this group Eight girls and 5 boys had bilateral adrenocortical hyperplasia. Two girls had this condition postnatally and two girls had bilateral adrenocortical adenomas.

Hormone-producing gonadal tumours One girl had granulosa cell tumour and 1 boy an interst tial cell tumour Following surgery complet regression of the signs of precocity occurred in the girl and only partial regression in the boy

Incomplete precocious puberty Isolated premature development of pubic hair without other signs of the onset of puberty were

found in 12 girls and 5 boys. Most of these children had severe congenital brain injury or brain injury resulting from birth trauma. Early development of pubic hair is not uncommon in mentally retarded children with severe brain injury In the children without brain damage, slightly increased androgen production by the adrenal cortex was probably responsible

Precocious breast enlargement. Isolated premature development of the breasts without other signs of the onset of puberty was found in 6 girls. This may have been the result of a constitutional tendency to increased susceptibility of the mammary glands to estrogen.

All 100 cases received a thorough clinical examination. Hormone titration, roentgen examination of the bones, electroencephalograms, *etc.* were done. The material is synoptically arranged, well worked out, and also includes good case histories. The conclusions of the investigation are based on factual conditions and are commendably free from loose speculation. This book is an outstanding contribution t a newly developing area of medicine.

Kurt Kaijser Eskilstuna

J Christophe Contribution à la biochimie des obésités expérimentales

Editions Arscia S.A., Bruxelles 1961

In the introduction to his report the author emphasizes the complex pathogenesis of human obesity and the difficulties of *approaching the problem in human beings.* In order to reach a better understanding of the biochemistry and physiology of obesity the author has chosen to study the biochemical relationships and the cellular physiology of adipose tissue in four types of bese animals. He has worked with (1) obesity *in rats on a high fat diet (2) the hereditary* obese-hyperglycemic syndrome in mice (3) obesity in "hypothalamic" rats and mice and (4) obesity in mice bearing an adrenocorticotropic tumor It is not possible in a short review to give a detailed account of the interesting results concerning the metabolic disturbances accompanying obesity It may however as an example be mentioned that rats on a semi-synthetic high-lard, carbohydrate-free diet had a greater increase in weight than the controls on a high-glucose diet in *spite of the same caloric intake* The author explains this as due to the fact that the direct storage of fatty acids requires less energy than lipogenesis from glucose. In the last chapter the author compares some aspects of "simple obesity" in human beings with those of the four types of experimental obesity investigated.

Dr Christophe s book is hiefly of interest to those who do experimental work on besity but may also be recommended to linicians who want t increase their know ledge of some of the fundamental and fascinating problems of this important disorder

C G Bergstrand

Ph. Schwartz Birth injuries of the newborn. S Karger Basel–New York. 384 pp. Price S.F 72.

Forty years of experience and systematical study of intracranial birth injuries have been condensed in a valuable monograph by the eminent pathologist. In his many former *original contributions and in the present* volume he has stressed the importance of parturitional abnormalities disturbing the regulation of vasomotor functions. This disturbance, when involving the *Galenic* system with the terminal and lateral ventricular veins of the brain, is of paramount *importance in the genesis of* intracranial hemorrhages and anoxic softenings of the brain. The book is easy to read primarily due to the arranging of most of the bibliographic material in a special section called "annotations" which allows presentation of knowledge and problems without the burden of too many historical notes and lengthy reviews of all previous investigations. A huge list of pproximately 3000 references is of a unique completeness. There are a number of photographs and drawings from autopsy material of somewhat varying quality including histopathological illustra

tions. For those engaged in the increasing efforts t lower perinatal mortality it is essential t have a clear picture of the pathogenesis of intracranial birth lesions contributing t a large extent t this mortality Such a knowledge is also important for those combatting the neurological sequelae in children surviving such injuries. The present volume offers excellent opportunities for pediatricians and obstetricians to gain this important knowledge.

B Hallström, Stockholm

ANNOUNCEMENTS

Nestlé Award for Pedology

The German Nestlé Company Frankfurt/Main, has given an ward of 3000:— DM for the best publication written in the German language within the field of the physiology of development in childhood (pedology) Applicants should send their publications as manuscripts or reprints in three copies not later than Sept. 30, 1963, to Professor F Linneweh, Universitäts-Kinderklinik, Marburg/Lahn, Germany The jury consists f three pediatricians from European countries. The ward will be made in Dec 1963. Articles published before the end of 1961 and/or written by authors who have been active professors at this time will not be considered.

Congresses

Nordwestdeutsche Gesellschaft fur Kinderheilkunde will meet in Hamburg April 27 28 under the chairmanship of Dr Kurt Erichson. Address Hamburg–Langenhorn, Kinderabteilung Allg Krankenhaus Heidberg, Germany The principal subjects to be discussed are: "N trition of healthy and sick infants and children and "Etiology frequency and treatment of malformations In addition there will be refresher course on Immunization against smallpox, t berculosis, DPT and poliomyelitis

A request

Professor S. A. Doxiadis of Athens University has asked for the publication of the following notice Are there any readers that can make a gift to the Hospital Aghia Sophia Athens of back volumes of Acta Pædiatrica that they may have in duplicate or that they may not require any longer Any donations should be sent direct to: The Library Children's Hospital Aghia Sophia Athens, Greece

The radioiron method

Theory After an intravenous injection of radioiron in tracer amounts the labelled atoms will undergo more or less complete mixing with the iron atoms of the body Some of the labelled atoms will enter the precursor pools for haemoglobin synthesis and will then be irreversibly incorporated into haemoglobin. The rate of appearance of the labelled iron in peripheral haemoglobin A and haemoglobin F will be a complicated and largely unknown function of the specific activity of the precursor pool, the rate of haemoglobin synthesis and the time course of maturation of precursor cells in the bone marrow Thus, by merely following the rate f appearance of the labelled atoms in the circulating haemoglobin no quantitative measure of the absolute rate of synthesis can be obtained However if it is assumed that the precursor iron pools are the same for HbA and HbF synthesis (cf. the discussion) and furthermore that the rate of maturation in the bone marrow is independent of the relative content of HbF in the cells, it follows that the ratio of the rat of appearance of the labelled atoms in circulating HbF and HbA must be equal to that of the rate of synthesis of the two haemoglobins. Since it is shown experimentally in the present work that the ratio

$$\frac{\text{Radioactivity in HbF}}{\text{Radioactivity in HbF and HbA}} \quad (1)$$

is constant with respect to time during the first 10–20 days after injection, any differences between the rates of change of the synthetic rates of HbF and HbA must be small during the period when the precursor pool is highly labelled. This period is short, of the order of a few days, both in normal adults and in infants (Garby Sjölin & Vuille, to be published) so that the estimate (1) obtained from several samples during the first 10–20 days after the injection actually refers to the rate of synthesis during the first few days after injection. Thus, the estimat (1) is a direct measure of the relative rate of synthesis of HbF and HbA at the time of injection.

Methods Radioactive iron (Fe^{59}) as citrat obtained from the Radiochemical Centre, Amersham, England was injected into a scalp vein in doses of 0.2–8.0 μC. The specific activity was about 2 μC/μg. The higher doses, bove 0 5 μC, were used in infants suffering from myelomeningocele or brain tumor Blood samples were then taken from heel punctures, usually 4–5 samples during the following 14 days. A haemoglobin solution was prepared from the washed red cells (Garby & Vuille [14]) and the radioactivity of this solution was measured in a well-type scintillation counter The detector was a Baird Atomic Model 810 B with an additional shielding of 10 cm of steel. HbF was then isolated and the amounts of HbA and HbF in the haemoglobin solution, as well as the amount of HbF in the filtrate, were measured according to the method described by Garby & Vuille [14]. As a rule, 4 ml of the HbF containing filtrate were counted. In some cases, where, for safety reasons, only small amount of Fe^{59} could be injected, the activity per unit f volume of th filtrate was too low to be measured with suff cient precision in spit of the improved separation method. In these cases, 10 to 20 ml of the filtrate were concentrated by salting out with ammonium sulphate and filtering through filter paper The filter paper was then placed in a plastic tube fitted to the detector crystal. The recovery by this method was found to be practically 100%. The radioactivity in the HbF present in the original haemoglobin solution was expressed as the percentage of the total radioactivity in the HbF and HbA. This estimat is, except for a factor of 100, identical with (1)

The coefficient of variation of a single determination of the percentage of radioactivity present in the HbF at any one time after injection was about 10% with no consistent time-dependent trend. Since the final estimate was based upon 3–5 single determinations, its coefficient of variation was about 5%.

The reticulocyte method

Theory It will be assumed here that the relative content of HbF in reticulocytes is a

TABLE 1

Subject	Pregnancy Normal	Pregnancy Pathol.	Maturity Birth weight g	Maturity Calculated gestational age	Delivery Normal	Delivery Pathol.	Condition of the infant during investigation Healthy	Condition of the infant during investigation Disease
Rm	+	—	3030	281	+	—	+	—
Vi	+	—	3130	263	–	Neonatal asphyxia	–	Cerebral tumor + haematoma subdur
I	+	—	3400	278	+	—	–	Myelomeningocele
R	+	—	3200	272	+	—	–	Myelomeningocele
Ban	+	—	3160	268	+	—	+	—
Eh	–	Tbc. pulm. sec.	4300	285	+	—	+	—
Ot		—	3170	283	+	—	–	Myelomeningocele
Li	+	—	2910	266	+	—	+	—
Ri	+	—	2700	277	+	—	–	Myelomeningocele
Sj	+	—	3310	303	+	—	+	—
Ls	+	—	2950	288?	+	—	+	—
Bj		—	3500	284	+	—	+	—
Kal	+	—	3010	294	+	—	+	—
J	+	—	3080	303?	+	—		Floppy child (+ urinary infection?)
F	+	—	4620	286	+	—		Convulsions
Gr	+	—	3710	270	+	—	+	—
P	+	—	3710	297	+	—	+	—
J		Proteinuria + hypertension	3010	280?	+	—		Myelomeningocele
L	+	—	4220	276	+	—	+	Cheilognatopalatoschisis

direct measure of the relative rate of synthesis of HbF. This assumption is correct if the life span of the circulating reticulocyte is invariant with respect to its content of HbF.

Methods. Reticulocyte smears were prepared according to Seip [22] with the exception that siliconized glassware was not used. After drying in air for about one hour and fixation in ethanol for 5 minutes, selective staining of the foetal haemoglobin was performed according to the method of Betke & Kleihauer [5]. One hundred to two hundred reticulocytes were examined and divided into four groups according to their relative content of HbF: group A comprised the reticulocytes which by their dark and homogeneous staining appeared to contain practically only HbF, the value being arbitrarily set at 90%, whereas group D included the "ghost" reticulocytes containing practically no HbF, the value being set at 0%. The intermediary forms were divided into two groups B and C, and the mean content of HbF was arbitrarily set at 60 and 20% respectively. The relative amount of HbF present in the whole reticulocyte population is then given by

$$\% \text{ HbF} = \frac{90\, n_A + 60\, n_B + 20\, n_C}{n_A + n_B + n_C + n_D} \qquad (2)$$

where n is the number of reticulocytes examined. All determinations were carried out by one person (J.-C. V.).

The error of a single estimate of the percentage of HbF in the reticulocytes was determined from 20 double determinations on 40 preparations. These preparations were labelled with coded numbers and were thus unknown to the examiner. The percentage of HbF in the reticulocytes in 17 of the preparations ranged between 17 and 56% and the error of a single determination was 2.6%. In the remaining three preparations, the results of the double determinations were 1.0–1.7, 5.6–6.7 and 4.0–6.0% respectively.

In each of the nine infants investigated by the reticulocyte and the radioiron methods, three or four estimations of the HbF in the reticulocytes were made.

The radiation dose

The radiation dose received by the different organs in these investigations was calculated according to the methods and data given by Loevinger, Holt & Hine [19]. Data on the distribution kinetics of the administered radioiron were obtained from the results in the present investigation and in two forthcoming publications (Garby, Sjölin & Vuille, to be published). For simplicity it was assumed that no excretion of radioiron occurred, since this assumption would only lead to an overestimation of the dose received. The critical organ in these experiments is presumably the bone marrow. This organ received about 0.5 rad during the first 13 weeks after the injection in the normal infants and about 2–3 rad in the infants with severe malformations. The dose delivered by the isotope after the first 13 weeks after injection is of the order of 0.1 rad in the normal infants. The other organs received a smaller radiation dose.

Results

The results of the measurements of the relative percentage of HbF present in the blood of the infants of the present series are shown in Fig. 1. These results are in agreement with data presented by previous investigators [4, 8], although it appears that our data show a somewhat smaller variation between the individuals. Of specific interest are Cases *Ja* and *Er* who show a consistently raised proportion of HbF in the blood.

The results of the measurements of the relative synthesis of HbF are shown in Tables 2 and 3. These tables contain all the primary data and serve to give an indication of the variations between the single estimates.

The relation between the two methods used to estimate the relative rate of HbF synthesis is shown in Fig. .. Each point

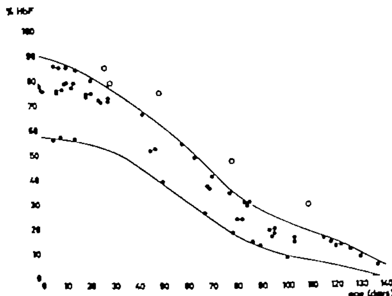


Fig. 1. The relative concentration of HbF in all infants and its variation with respect to age. The region between the curved lines contains 120 observations out of a total of 126 observations in the 17 normal infants. Case *J* ( ) and Case *Er* ( ).

in this figure represents mean values for one infant. Because of the fact that the reticulocyte studies were performed with time intervals that were not short with respect to the time constant for the decrease of HbF synthesis, the mean values of the reticulocyte method were corrected for this time lag, the correction factor being taken from the curve relating the relative HbF synthesis with age (Fig. 3).

The relative rate of synthesis of HbF as a function of the age of the infants is seen in Fig 3 Each point in this figure represents mean values for one infant. The curve in the figure is drawn by eye using all data, except the ones referring to Cases *Ja* and *E* These latter cases differ significantly from the remaining 17 cases in this respect also and will be discussed separately

Discussion

The theoretical basis of the reticulocyte method for assessing the relative rate of synthesis of HbF is presumably sound, and the precision of this method is quite adequate for the present purposes. In fact the precision is so high that this method, although developed in order to yield semi quantitative data, must be considered to give good quantitative data. The precision of the radioiron method seems to be high enough for most biological purposes. The theoretical basis for the radioiron method is correct if it is assumed that the precursor iron pool is the same for both HbF and HbA synthesis and that the maturation time of the precursors in the bone marrow is invariant with respect to their relative HbF content. Both assumptions are most reasonable since HbA and HbF are in all

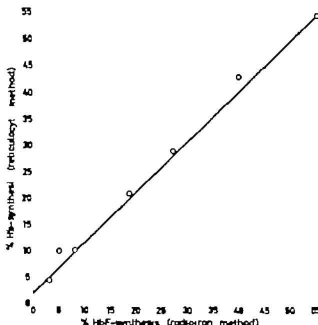


Fig 2. The relation between the two methods of measuring the relative rate of HbF synthesis in the nine cases, in whom both methods were used.

probability present concomitantly in the same cell (cf. this investigation and also Betke & Kleihauer [5] and Zipursky *et al.* [23]) The assumptions would not be correct if cells containing mostly HbF were formed in morphologically distinct parts of the body different from those where most HbA-containing cells are formed and if the respective precursor iron pools exchanged their iron with the plasma at different rates. Available evidence on the part played by different anatomical localities in the formation of HbA and HbF indicate [5 17 20] that there is no preferential site of formation of either of the two types of haemoglobin.

It is evident from the data presented in Fig 2 that the two methods developed to estimate the relative rate of synthesis of HbF and HbA are in very good agreement. This fact may be taken as good support for the conclusion that both methods give in fact reliable and quantitative measurements of the synthetic processes. The combination of both methods presumably increases both the precision and the accuracy of the estimation. The relatively large variation in relative HbF synthesis seen in Fig 3 is then most probably due to variations between the individuals themselves. This conclusion is borne out by the fact that there is also a relatively large variation with respect to the relative HbF content in the blood (Fig. 1), the estimate of which is based on a method with a very high precision.

The relative rate of synthesis of *HbF* is quite large at the time of delivery between 50 and 65 % of the total haemoglobin synthesis This figure is in good

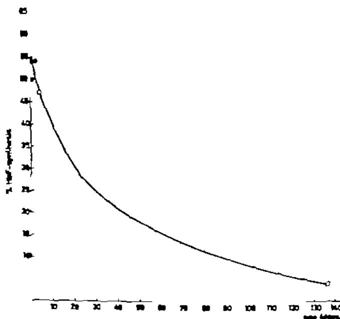


Fig. 2. The relative rate of HbF synthesis as function of age. Radioiron method ( ) and reticulocyte method ( ) in normal infants. Case *Ja* (radioiron method) and Case *Er* (radioiron method and reticulocyte method)

agreement with the data obtained by Dreyfus, Schapira & Harari [12]. These workers incubated cord blood with radioiron and measured the incorporation of this isotope into HbF and HbA. The ratio of the specific activities was 0.47 (mean value) and, since the relative amount of HbF in the samples was about 75 %, the relative rate of synthesis of HbF can be calculated to be about 60 %.

After birth, there appears to be rather abrupt decrease in the relative rate of synthesis of HbF during the first week or two and then a more gradual decrease towards very low values at the end of the 20th week. The absolute rate of synthesis of total haemoglobin during this age period is not known with any accuracy at present but studies on the relative decrease of the absolute synthetic rate of haemoglobin during the first weeks of life have indicated (Gardner Marks & Roscoe [13] Seip [21]; Garby Sjolin & Vuille, to be published) that this decrease is of quite a remarkable magnitude perhaps of the order of 3–10 times. Hence, the absolute decrease in HbF synthesis from the time of birth to the age of one or two weeks must be very large indeed.

Traces of alkali-resistant haemoglobin are always found in the blood of normal adults. Whether this type of haemoglobin is identical to that found in the newborn period is not quite clear [3]. Therefore it has not as yet been determined with certainty when or if the synthesis of HbF ceases completely.

Little is known about the stimulus for

TABLE 2 *The relative rate of synthesis of HbF as measured by the radioiron method.*

Subject	Age, days	Radioactivity in HbF 100 / Radioactivity in HbF and HbA — Days after injection of radioiron: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	Mean value
Ru	0	51		61				50								54
Ni	1		67			61			63							63
A	1		55		53		56				63				60	58
Be	1		44		51					50					53	50
Rus	2	56		54		52										54
Eh	3	46	40			35			37			38			39	39
Ol	3			69		63			63				64			65
Lö	5		54			44				58		51				50
Bl	7			57			53			55			51			53
Sj	15															23*
La	17		42		44				33			36				39
Bj	33		27				36			29				25		27
Rud	33		17			16		20								18
J	65		11				8.4			6.2				6.5		8
F	81		13		14				13				11			13
G	114	6.5			5.3		6.1		4.0				5.2			5
Ro	120				2.4		2.3		2.4				2.7			3
Ja	25		66		57				66				54			61
E	55		33				34			28				30		31

* Based on estimations on day 16 (24 %) and day 17 (23 %)

HbF synthesis in relation to HbA synthesis. The relative amount of HbF in the blood is undoubtedly correlated with the gestational age [1 10 11], in such a way that with increasing gestational age the relative amount of HbF decreases. Brody [6] has shown a remarkably high correlation between the gestational age and the estimated ratio of the relative amount of HbF to the birth weight. However all these facts are compatible with a constant or even increasing absolute rate of HbF synthesis. Bromberg, Abrahamov & Salzberger [7] showed that chronic, but not acute maternal hypoxia during labour was associated with increased relative concentrations of HbF in cord blood. Infants with congenital cyanotic heart disease did not show any consistent delay in the disappearance of HbF from their circulation [9].

Of the 19 infants investigated, two differed sufficiently to deserve special comment. Case *Er* had a low birth weight 2200 g, but a normal calculated gestational age, and was of normal length (49 cm). According to definition, she was thus a premature, but it seems more likely that the low birth weight was part of her aetiologically obscure malformation syndrome (cheilognatopalatoschisis and bilateral syndactylism of the fourth and fifth toes). She had a consistently elevated proportion of HbF in the circulation. It is interesting to note that she also had a relative HbF synthesis considerably in excess of that of the other children. Case *Ja* showed no signs of prematurity and his birth weight

TABLE 3 *Relative rate of synthesis of HbF as measured by the reticulocyte method*

Subject	Age days	% HbF in reticulocytes (cf. eq 3)
Bu	1	49
	3	46
	6	44
Kh	8	27
	12	28
	16	27
	18	24
Hud	40	16
	50	13
Bj	42	20
	46	20
	56	23
	60	23
Jo	74	7.8
	77	6.9
	83	6.2
	93	5.2
Fo	85	14
	88	9.4
	99	8.2
	104	12
Gr	115	2.9
	118	12
	120	11
	125	6.9
Ra	130	1.1
	133	6.3
	135	6.2
	140	2.8
K	68	30
	70	19
	75	21

and calculated gestational age were normal. However he also had a consistently elevated proportion of HbF in the blood and showed a large relative rate of HbF synthesis. The pregnancy was complicated by proteinuria and hypertension, factors which may have been of importance [illegible]

Summary

Two new methods for determination of the relative rates of synthesis of human globins F and A are described. One method is based on the relative rates of disappearance of intravenously injected radioactivity [illegible] circulating HbF and HbA. The other is based on estimates of the relative [illegible] of HbF and HbA in circulating [illegible] cytes. The two methods show good agreement.

The relative rate of synthesis [illegible] and HbA was measured in 19 [illegible] between 0 and 20 weeks [illegible] relative synthetic rate of HbF [illegible] 50–65 % of the total [illegible] thesis. After birth there [illegible] decrease in the relative [illegible] synthesis, but, even at [illegible] days, about 5 % of the [illegible] synthesis consisted of [illegible]

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Department of Pediatrics
University Hospital
Uppsala
Sweden

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From the Pediatric Department (Head. Professor A. Lambrechts)
Université de Liège, Belgium

Respiratory Studies in Children IV

Lung Volumes and Body Positions in Healthy Children

by F GEUBELLE[1] and C. GOFFIN

In a preliminary report [5] it was shown that the lung volumes including the functional residual capacity are modified by change of the body position in patients with poliomyelitis. Before undertaking a more extensive study of pathological conditions it seemed necessary to investigate the problem in healthy children and adults.

Definitions, Nomenclature nd Methods

The nomenclature used in this paper is the one proposed by a committee of respiratory clinical physiologists headed by Pappen heimer [1*]. The definitions and the methods have been described xtensively in a previous paper [6].

Briefly the functional residual capacity (V_{FRC}) is measured in a closed circuit system with helium as test gas; the inspiratory capacity (V_{IC}), expiratory reserve volume (V_{ER}) and vital capacity (V_{VC}) are measured by spirographic system without valves but equipped with fan-type pump [7].

All the alues are expressed in ml and corrected t body temperature ambient barometric pressure and saturated with water vapor (B.T.P.S.).

Material

The lung volumes were measured n nine pparently healthy children (16 determinations)· the time interval between two or three determinations in the same child was 1 to 4 days. For each assay the lung volumes were successively measured in the subject in the sitting, the supine and the prone posi tions. The time interval between each step of the assay was about 10 minutes. The total time used for one assay varied from 1½ to hours. The lung olumes were also mea sured (15 determinations) in nine apparently young healthy adults (five females and four males), ranging from 23 to 35 years of age by the same procedures as in children

Results

The mean values are given in Table 1 for the children and in Table for the adults. The individual differences in children and in adults between two successive determinations of V_{FRC} t 15 minutes interval in the same body posi tion were calculated. None of these dif ferences is significant

The random error of the method (standard deviation of differences between duplicate determinations divided by the square root of two) in the children is 58.3 ml in the sitting 59 5 ml in the supine and 04.3 ml in the prone position; this is 5.1 6 3 and 8.5 ,, respectively of the corresponding V_{FR} In the adults the error of the

[1] Aspirant Fond National de la Recherche Scientifique

TABLE 1 *Mean values ± error and standard deviation (S D) of the lung volumes in nine healthy children (16 determinations) in the sitting supine and prone position.*

	Sitting position			Supine position			Prone position		
	Mean	Error	S.D	Mean	Error	S.D	Mean	Error	S.D.
V_{FRC}	1,120	63	249	920	61	245	1 111	77	307
V_{VC}	2,295	139	554	2,206	129	517	2,263	139	585
V_{IC}	1 753	110	438	1,845	107	437	1,784	118	472
V_{ER}	541	54	215	361	41	164	480	61	242
V_{R}	586	36	144	568	43	172	590	66	262
V_{TLC}	2,880	137	549	2,776	137	548	2,857	161	645

TABLE 2 *Mean values ± error and standard deviation (S.D) of the lung volumes in nine healthy adults (15 determinations) in the sitting supine and prone position.*

	Sitting position			Supine position			Prone position		
	Mean	Error	S.D	Mean	Error	S.D	Mean	Error	S.D
V_{FRC}	2,600	173	670	2,308	170	656	2,640	172	664
V_{VC}	4,526	268	1 037	4,167	241	932	4,170	264	1,0 1
V_{IC}	3,355	220	891	3,672	221	858	3,187	223	903
V_{ER}	1 1 0	94	362	616	50	193	953	84	327
V_{R}	1,498	103	394	1,686	147	567	1,657	153	583
V_{TLC}	6,024	220	1,275	5,861	339	1,314	5,816	330	1,313

method is 103.9 ml in the sitting 102.7 ml in the supine and 123.5 ml in the prone position, this is 3 9 4 4 and 4 7 %, respectively of the corresponding V_{FRC}. The differences in lung volumes for each position (sitting minus supine, supine minus prone and sitting minus prone) have been calculated in each subject children (Tables 3 5 7 and adults, Tables 4 6 8)

When the difference is probably significant, significant or very significant,[1] the so-called "physiological variation"[2] is expressed in ml and in percentage of the corresponding mean lung volume in Table 9 Fig 1 and 2 illustrate the results.

Discussion

The average error of the method for the determination of V_{FRC} in the sitting position has previously been determined in this laboratory to be 7 % (range 1–4 %) of the corresponding mean V_{FRC} [8]. In the series presented here, the average error was 4.3 % in adults and 6.7 % in children. These values include the technical error of

[1] The probability is judged as follows (t test): $0\ 05 > P > 0\ 01$ is probably significant, $0.01 > P > 0\ 001$ is significant and $P < 0.001$ is very significant.

[2] "Physiological variation" is $\sigma_d/\sqrt{2}$ and $\sigma = \sqrt{S(x-\bar{x})^2/(n-1)}$.

Table 3. *Individual differences between the lung volumes in the sitting position minus the corresponding values in the supine position in children.*

M.D. = mean difference, E. = error and S.D. = standard deviation of differences.

	M.D.	E.	S.D.	P	"Physiological variation" ml	%
V_{FRC}	+201	33	150	0.001	−106	−9.4
V_{VC}	+88	30	122	0.012	−86	−3.3
V_{IC}	−92	42	169	0.044	+119	+6.7
V_{ER}	+180	36	145	0.001	−102	−18.8
V_R	+19	34	135	0.580	—	—
V_{TLC}	+107	43	170	0.024	−120	−4.2

Table 4. *Individual differences between the lung volumes in the sitting position minus the corresponding values in the supine position in adults.*

M.D. = mean difference, E. = error and S.D. = standard deviation of differences.

	M.D.	E.	S.D.	P	"Physiological variation" ml	%
V_{FRC}	+381	39	226	0.00	−161	−6
V_{VC}	+338	128	497	0.008	−331	−8
V_{IC}	−216	89	344	0.028	+244	+7
V_{ER}	+555	69	267	0.001	−189	−16
V_R	−183	71	270	0.022	+195	+13
V_{TLC}	+163	105	407	0.144	—	—

the whole apparatus (previously calculated as 1 %) and the changes of V_{FRC} which may vary slightly from test to test.

In general, the change from the erect to the supine position in adults produces a slight decrease in V_{TLC}, V_{VC} and V_R but a large decrease in V_{ER} with an inadequate compensation in the V_{IC} [3, 4, 9, 10, 13]. The decrease of V_{VC} (7.8 %) we observed in adults is about the same as has been calculated by others (4 to 7 %). In children, the observed decrease in V_{VC} is less than in adults and is only "probably significant" $(0.05 > P > 0.01)$. As far as we know no similar data in children have been reported. The increase of V_{IC} when changing from the sitting to the supine position is "probably significant" in adults as well as in children; the large decrease of V_{FRC} is "very significant" in both adults

Table 5. *Individual differences between the lung volumes in the supine position minus the corresponding values in the prone position in children.*

M.D. = mean difference, E. = error and S.D. = standard deviation of differences.

	M.D.	E.	S.D.	P	"Physiological variation" ml	%
V_{FRC}	−101	32	130	0.001	+92	+10
V_{VC}	−57	29	11	0.076	—	—
V_{IC}	+62	29	115	0.104	—	—
V_{ER}	−119	38	152	0.004	+104	+29
V_R	−64	45	178	0.162	—	—
V_{TLC}	−109	52	206	0.034	+146	+5

Table 6. *Individual differences between the lung volumes in the supine position minus the corresponding values in the prone position in adults.*

M.D. = mean difference, E. = error and S.D. = standard deviation of differences.

	M.D.	E.	S.D.	P	"Physiological variation" ml	%
V_{FRC}	−328	60	229	0.002	+162	+
V_{VC}	17	74	288	0.816	—	—
V_{IC}	+385	53	207	0.001	−146	−4
V_{ER}	−367	66	254	0.001	+160	+29
V_R	29	76	294	0.753	—	—
V_{TLC}	+46	[illegible]	[illegible]	0.356	—	—

TABLE 7 *Individual differences between the lung volumes in the sitting position minus the corresponding values in the prone position in children*

M.D = mean difference, E. = error and S.D = standard deviation of differences

	M.D	E.	S.D	P	"Physiological variation" ml	%
V_{FRC}	+12	42	167	0.780	—	—
V_{VC}	+31	29	115	0.294	—	—
V_{IC}	−30	37	150	0.438	—	—
V_{ER}	+61	39	157	0.143	—	—
V_R	−45	46	185	0.346	—	—
V_{TLC}	−7	40	161	0.884	—	—

TABLE 8. *Individual differences between the lung volumes in the sitting position minus the corresponding values in the prone position in adults*

M.D. = mean difference, E. = error and S.D. = standard deviation of differences.

	M.D.	E.	S.D.	P	"Physiological variation" ml	%
V_{FRC}	+29	73	262	0.686	—	—
V_{VC}	+356	110	434	0.006	−300	−7
V_{IC}	+168	90	348	0.088	—	—
V_{ER}	+187	83	320	0.042	−237	−19
V_R	−159	66	236	0.032	+181	+12
V_{TLC}	+208	80	349	0.022	−247	−4

and children. There is no significant change of V_{TLC} in our adult subjects; a probably significant decrease exists for children

To quote Brunton [2], many investigators are trying to find a key to the limitations which posture places upon breathing" [1 4, 9]. Measurements of the diameters of the chest of the radiological size of the thorax, of different lung volumes and of the mechanical properties of the lung have been made in an attempt to solve the problem

The findings suggest that the diminution of V_{VC} is mainly due to accumulation of blood in the lung and that a shift of the diaphragm accounts for the change in respiratory level and the inability to expire completely

In previous papers, attention was focused on the modifications of V_{VC}. The systematic measurements of the different lung volumes, presented here show that the changes of V_{FRC} are also important.

Few data are available for the lung volumes in the prone position. As shown

TABLE 9 *Changes of the lung volumes in three successive positions (sitting supine, prone) measured in nine healthy children and nine healthy adults*

The differences are expressed as "physiological variation" (see text) in per cent of the mean values in the sitting position for the first column, in the supine position for the second column, in the sitting position for the third column. The data between parenthesis changes probably significant (i.e. 0.05 > P > 0.01). The other data: changes significant (i.e. 0.01 > P > 0.001) or very significant (P < 0.001).

Lung volumes	Adults or children	"Sitting minus supine"	"Supine minus prone"	"Sitting minus prone"
V_{VC}	A	−7.8	0	−4.4
	C	(−3.3)	0	0
V_{IC}	A	(+7.3)	−4	0
	C	(+6.7)	0	0
V_{ER}	A	−16	+29	(19.4)
	C	−15.8	+29	0
V_{FRC}	A	−6	+7	0
	C	−9.4	+10	0
V_R	A	(+13)	0	(+12)
	C	0	0	0
V_{TLC}	A	0	0	(−4.1)
	C	(−4.5)	0	0

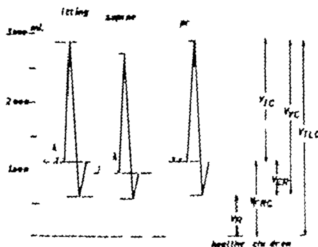


Fig. 1 Schematic illustration of the changes of the lung volumes with change in body position in healthy children.

in Fig. .., the values of the lung volumes of the adults in the prone position are nearer to the ones in the sitting position, the values recently found by Lagneau et al [11] lead to the same conclusions In children (Fig 1 Table 9) no significant differences were found between the values in the sitting and the prone positions.

Attinger [1] has calculated the values of the mechanical factors involved during the respiratory cycle the values for lung compliance in the prone position are

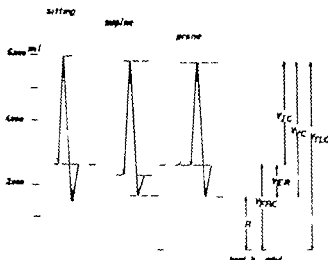


Fig. .. Schematic illustration of the changes of the lung volumes with change in body position in healthy adults

TABLE 7 *Individual differences between the lung volumes in the sitting position minus the corresponding values in the prone position in children*

M.D. = mean difference E. = error and S.D = standard deviation of differences

	M.D.	E.	S.D	P	"Physiological variation" ml	%
V_{FRC}	+12	43	167	0.780	—	—
V_{V}	+31	29	115	0.294	—	—
V_{IC}	−30	37	160	0.438	—	—
V_{ER}	+61	39	167	0.142	—	—
V_{R}	−48	46	186	0.248	—	—
V_{TLC}	−7	40	161	0.884	—	—

TABLE 8 *Individual differences between the lung volumes in the sitting position minus the corresponding values in the prone position in adults*

M.D. = mean difference, E. = error and S.D. = standard deviation of differences.

	M.D.	E.	S.D.	P	"Physiological variation" ml	%
V_{FRC}	+29	73	283	0.606	—	—
V_{VC}	+336	110	424	0.006	−300	7
V_{IC}	+168	90	348	0.066	—	—
V_{ER}	+187	83	320	0.042	−227	19
V_{R}	−169	66	234	0.032	+181	+1.
V_{TLC}	+208	80	349	0.022	−247	4

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Lung volumes	Adults children	"Sitting" minus "supine"	"Supine minus prone	"Sitting minus prone
V_{VC}	A	−7.8	0	−4.6
	C	(−2.3)	0	0
V_{IC}	A	(+7.3)	−4	0
	C	(+6.7)	0	0
V_{ER}	A	−16	+20	(10.0)
	C	−18.8	+[illegible]	0
V_{FRC}	A	−6	+7	[illegible]
	C	−8.4	+10	[illegible]
V_{R}	A	(+13)	0	(+12)
	C	0	0	[illegible]
V_{TLC}	A	0	0	(−4.1)
	C	(−4.2)	0	[illegible]

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From the University Clinic of Pediatrics (Head Professor P Plum) Rigshospitalet
Copenhagen, Denmark

A Follow Up Study of Children with Tics[1]

by ELSE TORUP

Because of the paucity of follow up studies of tics in childhood an investigation has been made whose aims were to study the prognosis of tics in childhood, as well as to determine if there are common characteristics among children with this disorder in order to further understand its genesis

Historical Review

There are only a few reports on the incidence of tics in childhood. In a child psychiatric clinic particularly interested in tics 3% of the children were referred for this reason [6]. Among a larger number of school-children, aged 10–11 years, tics were found in 4.8% of the boys and 2.6% of the girls [2].

Another author found tics in 23 % of school-children [1]. Tics are more common among children than among adults and are found twice as often in boys than girls [2, 6]. Although the etiology of tics has never been definitely established, they have been considered by at least one author to be the motor expression of psychogenic anxiety [4]. Over the years various forms of treatment have been tried, e.g. drugs, training of the muscles involved hypnosis and psychotherapy There is no agreement on the effect of such therapy whereas there is agreement on the value of living as normal life as possible More recently the importance of understanding and treating the causative factor rather than the symptom has been emphasized. Usually tics begin at about the age of 7 years and disappear later in childhood. Occasionally they continue throughout life Indeed cases with a poor prognosis lead to psychosis. The so-called "Maladie Gilles de la Tourette" [4, 5] is described in older literature but whether this is the same form of the disorder is not known.

Only a few follow-up examinations have been reported. After observing 33 patients for 1 3 years Zausmer [6] found that 23 % were cured. The criteria for cure was freedom from symptoms for at least one year The results were unrelated to therapy (lengthy psychotherapy or a few hours of educational guidance) although the patients tended to be selected beforehand, the most severe cases receiving the more prolonged therapy Boenheim [2] studied 31 patients 2 3 years after cessation of treatment about 65 % were free of tics and the remainder had improved

It is to be presumed that it is only the most severe cases that are treated by doctor and the reports mentioned therefore represent selected material with a poorer prognosis than the less serious cases.

Present Investigation

During the period 1946–1957 237 children with tics have been treated in the in or out patient services of the Rigshospital Pedia-

[1] The work was carried out with the support of Fonden til Lægevidenskabens Fremme

TABLE 1 *Sex distribution in the material from the various departments*

	I	P	O	B	Total
Total	31	119	26	44	220
Boys	19	89	19	36	163
Girls	12	30	7	8	57
Boys Girls	1.6:1	3:1	2.7:1	4.5:1	3:1

tric and Child Psychiatry Departments.[1] Two hundred and twenty of these children were followed up between May 1958 and May 1960 The length of observation time (counted from the first consultation in the Rigshospital to the time of follow up) varied from nearly 2 to 15–16 years with an average of about 9 years. The material includes patients in whom tics were diagnosed incidentally as well as those who were referred because of them.[2]

Information was sought concerning the features considered in the literature to be characteristic of children with tics as well as the various environmental factors. The information was obtained partly from the hospital records, occasionally supplemented by those from other hospitals. Personal interviews were conducted with 217 families and by letter in the three remaining families. In 26 cases the interviews took place at the Rigshospital, but in the majority (191) home visits were made, during which it was usually the mother who was interviewed although both parents in a few instances were seen. In most but not all cases the patient themselves were also interviewed.

In 1947 and 1948 an unusually large number of patients were referred. This may have been due to the insecure conditions during the war and immediate post war years. In many cases the tics were said to have arisen in connection with an air raid warning sabotage or other war action.

About 65% of the Pediatric Department patients were referred because of tics, whereas this was a secondary diagnosis in many of those from the Department of Child Psychiatry being the primary diagnosis in 23 % of out-patients and only 4% of in patients.

Results

Age and sex at onset of tics (Table I and Fig 1)

There is a predominance of boys in all groups, and in the whole series three times as many boys as girls. Tics began before the age of 10 years in 80–93% of the children from each department

Duration of tics before referral to the Rigshospital

There was a wide time-spread prior to referral (Fig 2) The mean duration was 1.9–3.0 years. As might be expected time before referral was the shortest in group P

Precipitating factors (Fig 3)

In more than one-third of the total group the precipitating factors were unknown. In the remaining 130 children the sudden occurrence of serious home conflicts (*vitium domesticum*) was by far the commonest factor

Previous treatment

Of 23 patients treated in the hospital, tics had temporarily disappeared in 6 and had become less marked in 3. Con-

[1] The head of the Child Psychiatry Department J Egsgaard, kindly allowed me to see the case records from his department.

[2] The group of patients admitted to the Pediatric Department are referred to as I and the out-patients as P From the Child Psychiatry Department the group of in patients will be referred to as O and the out patients as B.

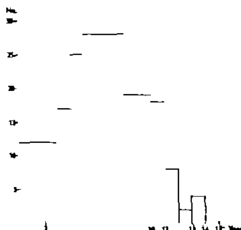


Fig. 1. Age at onset of tics in 208 of 220 children where this is known

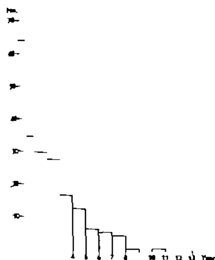


Fig. 2. Duration of tics before treatment at the Rigshospital in 207 patients.

valescent care in 14 had resulted in temporary disappearance of tics in 6 and diminution in one. Drugs and guidance in 45 patients had resulted in reduction of tics in 17.

Treatment in the Rigshospital

This was far more intensive and prolonged for the in patients. The duration of



Fig. 3. Precipitating factors in 220 patients. By vitium domesticum is meant the sudden occurrence of serious home conflicts; psychogenic factors means severe frights; somatic factors means an acute physical disorder

admission in both departments varied from a few weeks to 20–30 weeks with an average of 5 weeks for the Pediatric Department and 10 weeks for the Child Psychiatry Department. In contrast most of the out-patients came for only one or two visits. Fifteen patients received between 3 and 51 hours of therapy partly as out-patients. Drug therapy was rarely used.

In only a few patients were minor abnormalities which needed treatment diagnosed on physical examination. Treatment of these somatic disturbances had no effect on the tics.

Intelligence quotients were determined in 44 children and more extensive psychological testing including I.Q., in 72 others. The results of the latter are discussed later. Nineteen had an I.Q. of less than 90, 86 an I.Q. between 90–120 and 11 had an I.Q. of more than 130. The children not tested all appeared clinically to be of average intelligence and were managing to keep up normally in schools. The results of treatment of the in patients at the time of discharge can be seen from Table 2.

Among the out patients immediate cessation of tics following examination

TABLE 2 *Effect of treatment at the Rigshospital (in patients)*

	I	Tics at follow-up	O	Tics at follow-up
Tics ceased	7[a]	3	3[b]	0
Tics decreased	20[c]	11	7	3
Tics unchanged	4	3	6	4
No information			10	4
Total	31		26	

[a] 3 cases of recurrence.
[b] 1 case of recurrence
[c] Lasting improvement in 16 cases but no cessation.

TABLE 3. *Tics six months after cessation of treatment at the Rigshospital (out patients)*

	P	Tics at follow-up	D	Tics at follow-up
Tics ceased	16	0	11	
Tics decreased	20	10	9	6
Tics unchanged	83	52	23	16
No information			1	
Total	119			

5 cases of recurrence.

rarely occurred, but many children and their parents felt more at ease and the tics became less marked at once By investigation and advice one may perhaps have broken a vicious circle in which the parent's anxiety about the tics had been partly responsible for their continuance. In many cases it was not possible to pin point the time of improvement more precisely than from a few months to 6 months after treatment in the Rigshospital had ceased. The result of treatment among the out patients 6 months after discharge from the Rigshospital can be seen in Table 3

Treatment subsequent to that at the Rigshospital

About 40 % were treated elsewhere after discharge Tics disappeared in about 4 % and decreased in about 60 % of these. Treatment consisted of admission to hospital, convalescent care as a rule for 2–3 months, drug and other out patient treatment, as well as change of environment. It is difficult to assess which was the decisive therapeutic factor but parental guidance and environmental change are of importance. There have been no cases of tics disappearing on drug therapy (usually phenobarbitone) At the time of follow-up a lower incidence of tics was found among those who had not received treatment since their treatment at the Rigshospital than among those who had received further treatment, presumably because the more severe problems underwent further treatment.

Incidence of tics at the time of follow up (Fig 4)

The prognosis was the same in the four groups and among both sexes. About 50 % of the patients had been free from tics

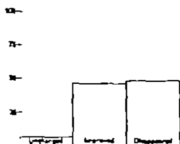


Fig. 4. Incidence of tics at the time of follow-up of 220 patients.



Fig. 5. Age at the time of follow-up of 220 patients.

for at least a year at the time of follow up and are considered cured. Another 46% were improved. Approximately 6% (14 patients) were unchanged but none were seriously incapacitated by their tics. Three of these children had borderline intelligence one was oligophrenic one had epilepsy combined with psychopathy and in the remainder five had severe home difficulties. This means that in 10 of the 14 cases circumstances existed which could, in all likelihood, explain the persistence of the tics Ten of the unchanged were older than 15 years at the time of follow up and the oldest was 4 years.

Age at the time of follow-up

This can be seen from Fig 5 The average age of patients with and without tics was the same about 18 years.

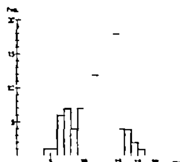


Fig. 6. Age at cessation of tics in 100 of 106 patients where it is known.

Age at cessation of tics (Fig 6)

The average age was practically the same in the four groups 1 -13 years. The duration of tics among those who were subsequently cured varied in the four groups, being shortest in groups P and B When taken as a whole most children had symptoms ranging in duration between 4.2 and 0.5 years In a f w cases tics lasted more than 10 years; the maximum duration was 14 years and the minimum one month.

Duration of tics which persisted at the time of follow up

The average duration of tics where symptoms had not disappeared at the time of follow-up was about 11 years (with an observation time of about 0 years) In bout half f the patients tics had lasted more than 10 years. The shortest duration was * years and the longest 1 years

Frequency nd local zation of t cs

At the time of the first consultation tics occurred daily in most of the patients. Some had them periodically for example only on a single day during a particular stress. At the time of follow up tics had

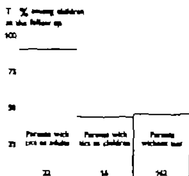


Fig. 7 Prognosis in relation t incidence of tics in parents of 200 patients with known predisposition. The figures within each box are the numbers of patients. Not that this figure refers only t parents, not to other family members with tics.

decreased in frequency and in many cases occurred only at times of special or intense stress. About 20–40 % nevertheless still had tics daily but in most of the patients the tics had decreased in intensity and area involved. Blinking and grimacing frequently remained after the other forms of tics had disappeared.

Tics in the family

These were found in about 30–40 % of the closest family members (parents siblings, grandparents, uncles, aunts, first cousins) In some families there were several cases of tics. Eleven to thirteen per cent of the parents had had tics in three of the groups, whereas in group O only 3 % had had them. In approximately half of the family members tics had persisted into adult life (≥20 years) The prognosis was worse among those patients whose parents had had tics as adults than among those whose parents had tics during childhood only (Fig 7) Furthermore there was a tendency to a higher incidence of tics in children with a family history of the disorder than where there was no such family history Among 63 patients with tics in the family 40 (64 %) had tics at the time of follow up whereas of 137 children with a negative family history 61 (45 %) still had tics.

In order to obtain a basis for comparison, 50 children picked at random from those admitted to the Pediatric Department of St Joseph s Hospital in 1960 have been questioned concerning the presence of tics in their families. Eight of the children (16 %) had either had tics in the past or still had them. Tics had been pronounced in only one of these. Among the 8 with tics there were 4 with tics in the family in 3 of whom they were in the parents. Among the 42 patients without tics there were 10 cases with tics in the family 4 of whom were in the parents

Nervous disorders were seen in from 80–100 % of the children at their first visit and in about 50–80 % at follow-up. Under this heading are included all types of behaviour disturbances, nervousness, nail biting stammering, anxiety sleep disturbance and delinquency In patients found to be nervous at the time of follow up there was a higher incidence of tics an thin those who were not nervous.

Psychological examinations

The psychological evaluation in 7 children, performed by a psychologist, Fru Wenja Rothe consisted in most cases of Rorschach and fable tests as well as the Thematic Apperception Test or Children s Apperception Test.

An overall evaluation of the children s psychological state revealed that there were great differences between one child and another both with reference to the degree of psychic damage and the type of

Table 4. *Characteristics.*

Restlessness	107 – 49
Sensitivity	171 – 78 %
Temperamentality	82 – 37
Anxiety	59 – 27 %
Less than normal self-confidence	82 – 37 %
Immaturity	60 – 27 %
Undue orderliness	60 – 27 %
No. among the latter group with compulsive behaviour pattern	26 – 12 %

conflict the children presented. Although there was a slight tendency to an accumulation of anxious and aggression hampered children in this series, a specific personality feature or structure common to a larger group of children could not be demonstrated. Similar conclusions were reached in an investigation of 28 children with tics, all with I.Q. more than 90, who were treated at the University Child Psychiatric Clinic during 1930–60.

A follow-up of these 28 patients resembling the present group, but supplemented by a new psychological examination, was planned but unfortunately could not be carried out. Contact during the required period was only possible in 10 families. This poor result must presumably be attributed to the fact that follow-up on this scale was very time-consuming for the patients, because it demanded several clinic visits from the patient as well as their relatives.

Some of the personality characteristics are tabulated in Table 4. As can be seen, increased sensitivity was a predominant feature.

Strained home conditions, for example indecisive, chronically ill or nervous parents frequently led to conflicts between parents and the child. Another apparently relevant feature was the frequent finding of poor living and economic conditions at the time of the first consultation (Table 5). There were more children with poor home conditions among the patients seen in the Child Psychiatry Department. At the time of follow up the situation had been rectified in many cases. In the children seen in the Pediatric Department the frequency of tics at the time of follow up was high among those patients whose home situation continued to be poor and was much lower where there were no home conflicts. This difference was not found in the patients from the Child Psychiatry Department, but the figures are small. Nervousness in the parents was

Table 5. *Serious home conflict*

	I (31)		P (119)		O (26)[a]		B (44)[b]	
First consultation	18	58 %	39	33	4	62	23	50
Follow-up	5	16	18	15 %	4	16	14	32
Tics occurring among the latter group	4	80	17	94	1	25	8	57
Follow-up, no home conflicts	26		101		22		30	
Tics occurring among the latter group	12	46 %	17	43	11	50	16	53 %
Average of tics		53		[illegible]		46		43

[a] patients in institutions at the time of follow-up
[b] patients in institutions at the time of follow up

TABLE 6 *Nervousness among parents*

	I&P (total 150)	O&B (total 70)*
Patient with nervous parents at time of first consultation	61 = 41 %	54 = 77 %
Patients with nervous parents at time of follow-up	58 = 39 %	38 = 54 %

* 13 patients in institutions at time of follow up

also a common finding (Table 6) possibly because all parents who described themselves as nervous are included.

The relationship of persistent tics to home conflicts, a family history of tics or other nervous symptoms in the family can be seen if one separates those patients to whom these factors apply from the total with persistent tics only a small number (13) remains.

Summary

Two hundred and twenty patients who had a history of tics were followed up 1–15 years after treatment in the Rigshospitalet. The age at follow up ranged from 6–26 years. Tics had disappeared in about 50 % and were unchanged in about 6 %. In the remainder the tics had decreased and were often insignificant. Tics often ceased at puberty. Among the cured, tics had lasted from one month to 14 years. In about half of the uncured, they had persisted more than 10 years. Restlessness and sensitivity were predominant features, although additional nervous symptoms were found in the majority. Nervousness was also common among the parents. In many instances, particularly just as the tics began there had been a serious home conflict. In 30–40 % there was a family history of tics. The prognosis with regard to the disappearance of tics was worse in those patients whose parents had had tics persisting into adult life.

There was a tendency for tics to disappear at the same time as other nervous symptoms and when home conflicts were resolved.

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Pediatric Clinic
Rigshospitalet
Copenhagen
Denmark

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From the Department of Anatomy Emory University Atlanta, Georgia, U.S.A.

Gastro-Intestinal Oxygen Insufflation in the Treatment of Neonatal Anoxia in Normo- and Hypothermic Guinea Pigs[1]

by BJÖRN WESTIN JAMES A. MILLER, JR. and ANN BOLES

If oxygen is introduced into the gastro-intestinal tract, it disappears by diffusion through the mucous membrane and is transported away by the circulation. The oxygen uptake through the stomach wall has been calculated to form about 5 % of the total oxygen uptake in unanesthetized human adults [14] Because the surface area of the small intestine is several times larger than that of the stomach, gastro-intestinal oxygen insufflation has been proposed as an aid in the treatment of asphyxia neonatorum [1 5 14] Since in asphyxiated neonatal infants, the foramen ovale should still be open because of apnea, oxygenated blood from the gastro-intestinal tract will pass without appreciable mixing from the right atrium into the left atrium [7 13] However animal experiments have shown that, if circulation is impaired which appears to be true in neonatal asphyxia absorption of oxygen from the intestines is markedly reduced [8] Measurements of oxygen saturation both in *normothermic* animals [4] and in one occasional premature [6] indicated that gastro-intestinal oxygen in sufflation was of no benefit.

Recently description was given of the use of hypothermia in the treatment of deep asphyxia of the newborn infant [11] Before hypothermia was induced, these infants were given artificial respiration and gastro-intestinal oxygen was administered. In spite of these therapeutic measures the condition of the infant deteriorated When hypothermia was induced by immersion of the body in cold water the infants gradually improved in condition although *artificial respiration* was omitted This might indicate that the gastro-intestinal oxygen administered prior to hypothermia although ineffective at normal body temperature became effective as the metabolic needs were lowered by cooling However this interpretation may be questioned, since neither skin nor pulmonary diffusion respiration was excluded. Since experimental evidence for the benefits of gastro-intestinal oxygen insufflation during hypothermic conditions appears to be lacking we considered it to be of some interest to study this

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Senior postdoctoral fellow from National Institute of Health, Bethesda, Maryland, U.S.A. Present address Women Clinic Sabbatsbergs sjukhus, Stockholm, Sweden.

Present address Department of Anatomy Tulane University New Orleans, Louisiana, U.S.A.

question. The present study is a report of the effects of gastro-intestinal oxygen insufflation in the treatment of neonatal anoxia of normothermic and hypothermic guinea pigs in which oxygen uptake through the skin and lungs was eliminated.

Material and Method

Anoxia equipment

A chamber was made with three walls and ceiling of plexiglass with dimensions 11 × 16.5 7 inches. One side wall was made of common sheet glass to allow transmission of radiant heat from a heating lamp outside the chamber This heat source was used to prevent drop in body temperature during the exposure to anoxia. The chamber had 2 ports t each end, 6 inches in diameter These entry ways were fitted with sleeves from an 'Isolette incubator which provided an air tight cuff for the operator s arms.

The gas used was pure nitrogen. The tank was fitted to a common flow regulator and connected to a plexiglass pipe in the ceiling of the chamber especially designed for rapid mixing of gases. The gas escaped through the floor which consisted of a 0.25 inch thick sheet of foam rubber Before each experiment started, the chamber was flushed with nitrogen gas at an increased flow rate for one minute and then maintained at a flow rate of about 15 liter per minute throughout the experiment. In ea h case, about 3 minutes elapsed between the onset of flushing of the chamber and the start of the animal experiment.

Method for gastro-intestinal gas insufflation

A 10 ml syringe with glass plunger and minimal leakage was selected. Before use, the plunger and barrel were greased carefully with white petroleum jelly to prevent leakage. A Pharmaseal premature feeding tube (Fr 8) with smooth rounded tip was att ched t the syringe with the plunger disconnected. The plastic tube was attached to a nitrogen tank and the syringe was flushed with the nitrogen gas. The plunger was introduced into the barrel and the catheter disconnected from the gas tank. The gas volume in the syringe was adjusted to 4.0 ml at atmosphere pressure. The catheter was immediately clamped by means of a tourniquet, and the open end of the catheter was sealed by dipping it into petroleum jelly Before the experiment started, the syringe was placed inside the nitrogen chamber When the animal was exposed to nitrogen, collapse occurred between 15 and 30 seconds from onset of exposure. At this time the plastic tube with the syringe attached to it was introduced into the stomach via the mouth. An animal was selected as a normal control. Exactly 2.0 minutes from onset of the experiment the tourniquet was released and the nitrogen gas contained in the syringe was injected into the stomach. The catheter was left in the stomach connected to the syringe throughout the period of anoxia. With its litter mate the procedure was similar but instead of nitrogen, 4 ml of oxygen were injected into the stomach. To test whether or not retrograde leakage occurred upon injection of 4 ml of gas into the stomach, some experiments were performed on dead newborn animals kept under water If the catheter was too thin or not introduced as far as the stomach, part of the gas leaked backward. Such leakage did not occur ith the catheter used in the present experiments. On autopsy after the experiments, the gas distended the stomach and at least the proximal half of the small intestine

The Experimental Animal

A total of 140 apparently healthy guinea pigs about 12 hours old from a well inbred colony were used. In 40 experiments litter mate pairs were used and in 20 experiment litters of three. The animals were starved before the experiment. Their rectal temperatures were taken with a Yellow Springs Inst Co. Tele-thermometer The thermistor was inserted about 2.5 cm int the rectum and the temperature was checked before during and after the experiment In general the rectal temperature did not fall more than 0.2°C in any of the experimental groups.

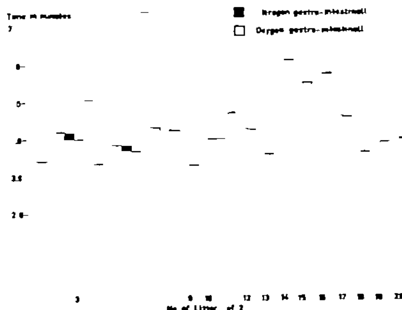


Fig. 1 Time of last gasp of normothermic neonatal guinea pigs breathing nitrogen. *Litters of 2.*

Time of last gasp in normothermic guinea pigs

The final gasp on exposure t nitrogen gas is suitable measure of anoxic resistance [7]. The point of time can be defined with an accuracy of less than one second and after the final gasp the animals do not recover spontaneously in air If gastro-intestinal oxygen had been absorbed and transported t vital organs in ppreciable amounts, the gasping time would be significantly prolonged in comparison with animals treated with nitrogen gastro-intestinally

The group investigated comprised "0 litters of 2 (40 animals). Before the experiment all animals had a body temperature f 37 C as measured by deep colonic temperature. In some instances artificial warming was required t reach the desired temperature Both littermates were exposed t nitrogen in the chamber one animal received nitrogen and the other oxygen gastro-intestinally The time of the final gasp was determined for both animals and a paired comparison wa performed.

Time of last gasp n hypothermic guinea pigs

This group comprised 20 litters f (40 animals). Before being subjected t anoxia, body temperature, measured high in the colon was reduced to °T°C by immersion f the body in cold water (4–6°C) After the desired body temperature was reached, the fur was dried.

The procedure was similar t that of the normothermic group. The first litter-mate received nitrogen and the second oxygen gastro-intestinally Their final gasping times were determined and compared.

Recoveries by hypothermic gu nea pigs

This experimental group consisted of "0 litters f 3 (60 animals).

Before being subjected to anoxia, body temperature was reduced to 27°C The first litter-mate was put in the nitrogen chamber and the time for it final gasp was determined. No other treatment was given. The time for the final gasp of this animal then served anoxic exposure time for litter-mates nos.

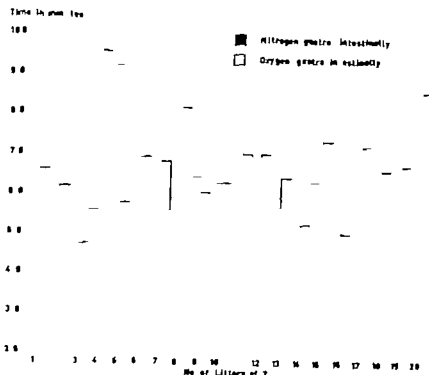


Fig 2 Time of last gasp of hypothermic neonatal guinea pigs breathing nitrogen. Litters of 2

and 3 No received nitrogen and no 3 oxygen gastro-intestinally and were left to recover spontaneously in ai Animals were judged to have survived the experiment if they were alive 24 hours later

Results

Time of last gasp in normothermic guinea pigs

The elapsed times until the final gasp of each pair of litter mates are indicated in Fig 1 In general it can be said that the gastro-intestinal oxygen therapy had no observable effect on any of the animals. The mean time for the last gasp of all animals treated with nitrogen gastro-intestinally was 4.30 ± 0.24 (ε) minutes The corresponding figure for all animals treated with oxygen was 4.22 ± 0.16 The difference between the groups is insignificant. Utilizing the smaller biological variation in a paired comparison between litter mates of the elapsed time until the last gasp the animals treated with oxygen lived 2.4% longer than their controls. This increase is insignificant. In the group of animals treated with oxygen gastro-intestinally 10 animals lived longer and 10 shorter than their controls, which is consistent with distribution by chance Thus the conclusion can be drawn, that, under the present experimental conditions, gastro-intestinal oxygen insufflation does not postpone death in normothermic guinea pigs, breathing nitrogen.

Time of last gasp in hypothermic guinea pigs

The elapsed times until the final gasp of each pair of littermates are shown in Fig 2

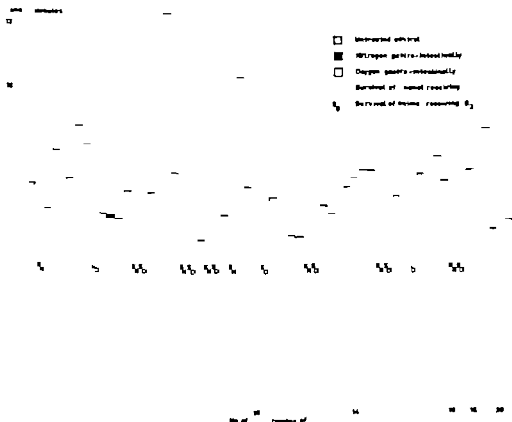


Fig. 3. Time of last gasp of hypothermic neonatal guinea pigs breathing nitrogen. Litter-mates of 3.

Attention is first drawn to the fact that the mean time of the last gasp for all hypothermic animals receiving nitrogen gastro-intestinally was 6 01 ± 0.25 (s) minutes. When this figure is compared with the corresponding figure for normothermic animals, it is found that 10°C red ction in body temperature prolonged the time for the last gasp 40 ᵒ/ (P < 0 001). The mean value for the time of the last gasp of all hypothermic animals receiving xygen gastro-intestinally was 6 70 ± 0.24 minutes. The difference between thi group and its hypothermic control group wa 0 69 minutes (P ~ 0.03).

Utilizing the smaller biological variation in a paired comparison between litter mates, the animal treated with oxygen lived 15 8 longer (0 01 < P < 0 001) than their controls. Among animals treated with oxygen, 14 (ᵒ0 ᵒ/) lived longer than the former group. In conclusion t can be said that a 10°C reduction of body temperature a a ingle factor significantly postponed death a determined by the last gasp, in comparison with normothermic controls. It is lso probable that gastro-intestinal xygen administration during hypothermia postponed the time of death in comparison w th hypothermic control. In

order to test whether or not gastro-intestinal oxygen insufflation during hypothermia might be a life-saving measure the following experiments were performed.

Recovery of hypothermic guinea pigs

The results are graphed in Fig 3 where the times of last gasp are given for untreated controls and non-surviving litter mates treated with gastro-intestinal nitrogen or oxygen. An open space (S) between columns indicates that the litter mate survived. The mean time for the last gasp of all untreated controls was 6.69 ± 0.20 a significant ($P < 0.001$) lengthening of time in comparison with the normothermic guinea pigs and apparently related to the reduction in body temperature Nine guinea pigs recovered (45 %) after receiving nitrogen gastro-intestinally and breathing nitrogen for the same period of time as their untreated litter mates. The corresponding figure was 10 (50 %) for the group of animals treated with oxygen gastro-intestinally indicating that the therapy had no significant influence on the survival rate. However the same trend was found among the animals that died, with regard to the time of last gasp as in the foregoing hypothermic experiments on litters of 2 The 11 animals receiving gastro-intestinal nitrogen gave their last gasp at a mean time of 6 93 ± 0.25 minutes, while the corresponding figure for the 10 animals receiving oxygen gastro-intestinally was 7 63 ± 0 49 minutes Utilizing paired comparison the guinea pigs receiving oxygen gastro-intestinally gave their last gasp 9.2 % later ($P < 0.05$) than their litter mates receiving nitrogen gastro-intestinally

In conclusion it can be said that, although gastro-intestinal oxygen therapy probably postponed the time of the last gasp this effect was not enough to prevent death from anoxia under the conditions of these experiments.

Discussion

Neonatal guinea pigs were used in these experiments because of the large amount of information which has been assembled both on the effects of asphyxia in the newborn of this species [1-9] and on the influence of temperature upon asphyxial survival [9 10] The prolongation in the time of last gasp in the hypothermic as compared with normothermic control litter mates in these experiments was of the same order of magnitude as reported for guinea pigs asphyxiated in 95 % N_2 + 5 % CO_2 [9]

Since the failure of gastro-intestinal insufflation of oxygen as a resuscitative measure in these experiments might be the result of the use of an inadequate volume of the gas, an estimation was made of the length of time that 4 ml of oxygen would support life for a newborn guinea pig Measurements determined that the oxygen uptake of normothermic newborn guinea pigs (at 39°C) was 3 1 ml/100 g/min and for the same animals when cooled to °1 was 1.5 ml/100 g/min [10] Adjusting these figures for an average 75 g animal at 37°C and disregarding the fact that hypoxia itself depresses oxygen utilization, 4 ml should prolong survival approximately * minutes in the normothermic and about twice as long in the hypothermic animals. Thus, the final gasp might have been postponed markedly in the normothermic animals had sufficient amounts of oxy

genated blood reached the central nervous system. Since this did not occur neither in the present nor in previous experiments [4–6], the failure of the therapy might be explained by circulatory impairment or by large oxygen consumption by the liver. In all likelihood both of these factors were operating simultaneously. This assumption is supported by autopsies begun immediately after the final gasp. The veins draining the small intestine usually had a lighter red color when oxygen had been inflated but independent of whether oxygen or nitrogen had been administered, the blood in the right atrium was always extremely dark.

In the hypothermic guinea pigs the gastro-intestinal oxygen treatment probably postponed death, even if no increase in recoveries could be demonstrated. These results on guinea pigs are not directly applicable to the human infant, since the latter is less mature, resists anoxia better and consequently reaches a stage of circulatory insufficiency later. Because of these differences in circulatory response to anoxia, the improvement noted in hypothermic infants [11] following inflation of the gastro-intestinal tract with oxygen may not be inconsistent with the present results in hypothermic guinea pigs. It can, however, not be excluded that retrograde leakage of oxygen and simple diffusion respiration of the lungs [2], may play some role in the recovery of the hypothermic infants. However, since the newborn guinea pig is the most susceptible to asphyxiation of any species which have been tested, the time during which anoxic effects may be reversible is very limited indeed. It is possible that similar experiments upon newborn puppies, whose asphyxial resistance resembles more closely that of neonatal human infants, might show significant differences in recovery between *hypothermic* experimental and control animals.

Summary

The effectiveness of gastro-intestinal insufflation of oxygen in the treatment of neonatal anoxia was tested in 40 normothermic and 100 hypothermic newborn guinea pigs in experiments in which oxygen uptake via the skin and lungs was prevented.

1. In normothermic animals gastro-intestinal insufflation of oxygen did not postpone death from anoxia induced by exposure to 100% nitrogen.

2. Hypothermic control animals, receiving nitrogen gastro-intestinally, lived significantly longer in nitrogen than did normothermic animals, whether they were insufflated with nitrogen or with oxygen.

3. The time of last gasp for hypothermic animals insufflated gastro-intestinally with oxygen was postponed as compared with that of control littermates insufflated with nitrogen. However, the benefits of the treatment were not sufficient to permit spontaneous recovery from an exposure which was lethal for control animals at the same temperature.

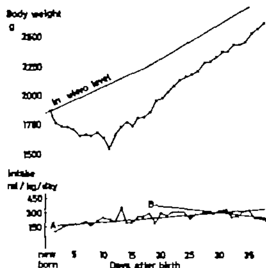


Fig. 1 Example of an infant whose intake in ml/kg/day is seen to rise during the first 25 t 30 days of life (graph A) and fall in the last week of life (graph B) The weight of the baby remained below the *in utero* level at all times.

was ordered in four infants under six days old. The length of time the infants nursed usually ranged from five to 30 minutes, oc casionally up to one hour Supplementary water feedings were only rarely given.

A prepared milk formula was used. Seventy four of the infants received regular formula throughout their nursery course, 119 received concentrated formulas, and 26 received both regular and concentrated formulas. The regular dilution of the milk contained 17 t 20 calories per 30 g, and the concentrated form contained from 33 to 40 calories per 30 g Both the liquid and the powdered form f the prepared milk were used t first but only the powdered form was used during the latter part of the study because of the occasional development of loose stools in infants who received the liquid form at a concentration of 40 calories per 30 g. Loose stools were not seen when con centrated formulas containing from 33 to 34 calories per 30 g were used.

The body weight was determined daily using scales which were accurate within 5 g. The weights were determined just before feeding, but the time of weighing was not controlled in relation to voiding or the passage of stool.

The body weights are drawn in relation to the *in utero* rate of weight gain, as calculated from the data f Scammon [3] and Ylppö [5]. Observations on the 219 infants reported were made from birth until they attained a weight of from 450 to *650 g at which time most of the infants were discharged.

Method of analysis of data

The daily intake in ml/kg/day was plotted and regression lines were drawn through the multiple points to establish whether the intake was increasing or decreasing (see example Fig. 1) The day of life when the intersect of two graphs occurred was noted and related to the weight of the infant had he remained *in utero*

Results

During the first few days of life the intake in ml/kg/day of premature infants invariably increases (see examples, Fig 1 4) During this time it is relatively independent of the concentration of the for mula used (see example Fig 2) Later in the nursery course a decreasing intake occurred in 56 % of the infants whose body weight reached the *in utero* level (see example *Fig 3* and *Table 1*). A decreasing intake was observed in only 16 % of infants whose weight did not reach the *in utero* level. The statistical significance of this difference has a *P* value less than 0.01 A decreasing intake was relatively independent of the concentration of the for mula that was used (see Table 1). Babies with a birth weight under *000 g had a decreasing intake more frequently than those who weighed over *000 g This was

Similac (R) manufactured by the Ross Laboratories, Columbus, Ohio, was used in these studies.

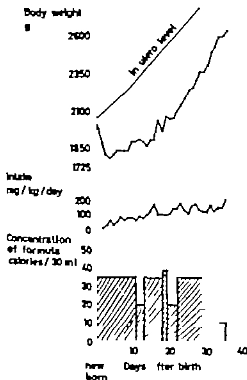


Fig. 2. Finding in an infant in whom the caloric concentration of standard formula was altered from 12 to 50 calories per 30 g. The intake in ml/kg/day rose progressively throughout the nursery course independent of the caloric concentration of the formula used. The body weight remained below the *in utero* level at all times. The baby is not one of the 219 consecutive infants reported in Table 1.

primarily related to whether the infants weight reached the *in utero* weight level. Possibly the longer nursery course and adjustment to extrauterine life accounts for the small residual difference not related to the weight status of the infant.

Eighty five per cent of premature infants whose body weight remained below the *in utero* level had either an increasing intake or a high level of intake (plateau) which was sustained throughout the nursery course whereas only 15% of the infants whose body weight remained below the *in utero* level had a decreasing intake. The level of significance of this difference has a P value less than 0.01 (see Table 1)

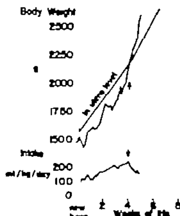


Fig. 3. Example of an infant whose intake in ml kg/day falls when the body weight exceeds the *in utero* level (see arrows).

The character of the intake (i.e. increasing or decreasing) in the 219 consecutive premature infants is summarized in Fig 5 In 71 of these infants, the *in utero* weight level was attained and in 148 the body weight remained below the *in utero* level. The intake fell much more frequently in the infants whose body weight reached the *in utero* level than in the infants whose body weight remained below the level.

Discussion

The voluntary intake in ml/kg/day of "healthy"[1] premature infants is partly dependent on the frequency of feeding, and on the time allotted for each feeding In the present observations, the infants were fed relatively frequently and were

[1] Health refers to the absence of over clinical disturbances.

TABLE 1 *Studies in ad libitum feeding The voluntary intake in ml/kg/day of 219 premature infants during their nursery course.*

Highly significant differences ($P < 0.01$) were as follows. *A decreasing intake* was found more frequently in infants whose body weight returned to the *in utero* level than in those infants whose weight remained below the *in utero* level. *An increasing intake* was found more frequently in infants whose body weight remained below the *in utero* level than in those infant whose body weight returned to the *in utero* level. Some infants were fed both regular and concentrated formula and these infants are not included in the columns headed "Type of formula. Therefore, the number of infants in the columns headed "All infants" is greater than the number of infants in the columns headed "Type of formula.

Intake, ml/kg/day	Infants whose body weight reached the *in utero* level					Infants whose body weight did not reach the *in utero* level				
	All infants	Type of formula, calories per ml		Birth weight, g		All infants	Type of formula, calories per ml		Birth weight, g	
		0.67–0.67	1 1–1.3	<2000	2001–2500		0.67–0.67	1 1 1.3	<2000	2001 250
No. Pts.	71	19	45	53	18	145	55	74	34	114
Increased during entire nursery course	15.5%	10.6%	20%	15.1%	16.7%	55.5%	63.6%	55.4%	35.3%	62.2%
Increased and then remained stationary	28.2%	36.8%	15.6%	24.5%	38.9%	28.7%	20.0%	31 1%	41.2%	24.6%
Increased and then fell	56.3%	52.6%	64.4%	60.4%	44.4%	15.8%	16.4%	13.5%	23.5%	13.2%

allowed to feed on each occasion until they stopped. Thus, the two chief exogenous factors which effect the voluntary intake

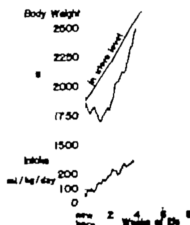


Fig. 4. Example of an infant whose intake in ml/kg/day increases rapidly at all times; the weight of the infant remained below the *in utero* level.

of premature infants were controlled. The finding that there is a reduction in the intake in ml/kg/day in a much higher percentage of infants whose body weight reached or exceeded the *in utero* weight level than in those infants whose body weight remained below the *in utero* level can be explained as follows. The premature infant, who may be nutritionally deficient, drinks as large a *volume* of milk as possible. His gastrointestinal capacity for volume increases progressively or until a maximum capacity is reached. When his nutritional deficiency is corrected, his volume (and therefore caloric) intake in ml/kg/day is "voluntarily reduced. This explanation requires the assumption that the *in utero* rate of weight gain bears a *relationship* to the normal

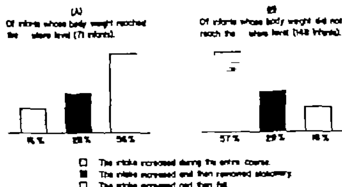


Fig. 5. The character of the intake in 219 consecutive premature infants.

(physiologic) nutritional status of the premature infant during his uterine existence. In the absence of a more reasonable yardstick of "normal" nutrition, this assumption cannot be discarded.

In fact, it is quite probable that nutritional deficiency occurs in many premature infants who have almost no fat which can be used for energy and who have a caloric intake which is usually grossly deficient in the first few days or weeks of life [.., 4].

Fifteen per cent of the premature infants who were fed with the modified *ad libitum* regimen appeared to eat "too much" as manifested by their gaining weight at a rate which was in excess of the *in utero* rate (see Table 1). One cannot be sure that infants who gain more weight than is predicted by the *average in utero* rate of weight gain would not have been bigger (or fatter) than average had they remained *in utero*. Some normal full-term infants are quite fat in appearance at birth. Another possibility is that they suffered from malnutrition (placental insufficiency) while they were *in utero* and then regained this weight after birth. Some of these infants also might have become "over nourished" especially when the body weight eventually far exceeded the average *in utero* level (see example Fig 6). There are no criteria which can be used to decide which of these mechanisms may be operative.

Conversely 16% of the premature infants had a decreasing intake before their body weight reached the *in utero* weight

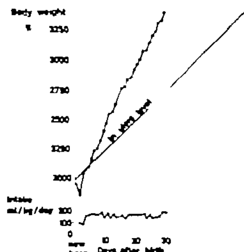


Fig. 6. The intake in ml/kg/day of an infant whose body weight rose markedly over the *in utero* level. This patient in contrast to the majority of infants whose body weight reached the *in utero* level, continued to have a fairly high volume intake.

level (see example Fig 1) It cannot be ascertained whether these infants might normally have been smaller or thinner than average or whether some obscure disorder interfered with their taking a larger food intake. An alternative possibility is that some of these infants do not have an appetite center responsive to the needs of normal nutrition

Edema and hypohydration would tend to obscure the relationship of the character of the intake (i.e. whether increasing or decreasing) to the weight status as compared with the *in utero* weight level. However gross disturbances in hydration were not clinically apparent, except occasionally in the first week of life. At this time the intake–weight status relationship under consideration is not being evaluated, since all infants at this age have an increasing intake. However edema and hypohydration, if present at birth, would falsely raise or lower respectively the true birth weight and therefore tend to obscure the basic point of reference from which the *in utero* weight grid is drawn. Possibly this is one of the factors which partially obscures the point being evaluated.

In a recent editorial "Hunger and Appetite" by Janowitz [1] data relating to voluntary intake were analyzed in relation to the possible mechanisms involved. This author favors the view that "what is being regulated or corrected in the long run is the body's store (excess or deficit) of nutritional elements" The present data pertaining to premature infants may be similarly interpreted

Summary

Premature infants ranging in weight from 1106 to 2500 g were assigned to a modified *ad libitum* feeding regimen. Their volume intake in ml/kg/day increased for the first few days of life and usually reached a plateau of from 200 to 350 ml/kg/day A *decrease* in the intake was observed in 56 % of the infants whose body weight reached or exceeded the *in utero* level but in only 16 % of the infants whose body weight did not reach the *in utero* level. The rate of weight gain of the fetus *in utero* was calculated from the data of Scammon and Ylppö

Conversely 85 % of the infants whose body weight remained below the *in utero* level had an increasing intake or a high level of intake throughout their nursery course. Only 15 % had a decreasing intake The probability that these differences were due to chance is exceedingly small ($P < 0.01$)

The data are interpreted to indicate that many premature infants have an appetite center which is responsive to the physiologic need of normal nutrition.

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Department of Pediatrics
The Jefferson Medical College of Philadelphia
1025 Walnut Street
Philadelphia, Penna.
U.S.A.

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From the Department of Pediatrics, Karolinska Sjukhuset Stockholm

The Thermogenic Response of the Newborn Infant to Noradrenaline[1]

by P KARLBERG R. E. MOORE[2] and T K. OLIVER, Jr.[3]

The newborn human infant may respond to a change in environmental temperature by an alteration in its heat production [4 17] This response is a thermoregulatory mechanism which serves to maintain *thermal equilibrium under conditions* where control of heat loss is not of itself adequate to do so Similar thermoregulation has been observed in several animal species [9 10 16] and occurs at temperatures lower than what is termed the neutral zone

It has been suggested [13 14] that noradrenaline (NAd) could be the mediator by means of which heat production is controlled in the newborn. This substance has also been invoked as the thermogenic hormone in cold adaption in adult rats [6, 7 11 12] *A direct test of the hypothesis* that noradrenaline had this thermogenic action in the human newborn was obviously of great interest and importance since a better understanding of the control of heat production in the infant could be of considerable clinical value

Methods

Oxygen consumption and CO_2 output were measured by an open circuit method using the Noyons Diaferometer[4] readings being taken every minute The lag time of the apparatus was about 2 min for CO_2 and 3 min for O_2. The accuracy of the method had been checked previously by alcohol tests. Agreement was better than ±3% in each of a series of tests performed over several months. The random error of the method calculated from the difference between two 10-minute periods 8 to 30 min part was ±3 8%. All values were corrected to 0 C 760 mm Hg, dry (STPD)

Room air was drawn past the baby at constant rate of either *4.50* or *2.80 l min*. The baby was covered to about knee level by a transparent hood arranged so that the incoming air passed along the trunk to the head end from which it was extracted to the analyser The hood was 50 cm long and 15 cm high; the head end was closed except for the extractor outlet and the other end terminated in a soft plastic sheet which was tied loosely about the baby's knees. The baby in its hood was placed in a temperature-controlled incubator allowing constancy of hood temperature to within ±0.5°C.

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[1] This study was supported in part by grant from the Association for the Aid t Crippled Children as well as a Special Fellowship (BT 362) of the National Institut of Neurological Diseases and Blindness, Public Health Service USA (TKO).

[2] Department of Physiology Royal Free Hospital School of Medicine London WC 1 England.

[3] The children Hospital, Columbus 5, Ohio, USA.

[4] P J Kipp & Zonen, Delft Holland.

Hood temperature is the en ironmental temperature of the baby above knee level. Cotton stockings were put on the feet and lower legs, which, being outside the hood in the incubator were t temperature of about 3°C (limit 1 –6 C) lower than the hood.

Temperatures were measured using thermocouples. One was placed 4–5 cm deep within the rectum, another on the sole of the right foot over the first metatarsal head, others were suspended within the incubator and inner hood. Temperatures were recorded at intervals of 1 to 5 min. The absolute accuracy of the thermocouple assembly was better than ±0.1°C checked against a certified thermometer.

A direct-writing ECG recorder (Mingograph 42, Elema) monitored heart rate continuously from electrodes on the precordium and the thighs. Heart rates were determined as required, every ½ to 2 min by measuring the time for 40 beats.

Noradrenaline (Nor-exadrine, Astra) was made up in a sterile 2% dextrose–0.45% NaCl aqueous solution and infused at a constant rate using a syringe driver through a polyethylene catheter 1.5 mm outside diameter in the umbilical vein. The catheter was normally inserted to a depth of 10–12 cm, so that the tip lay within the inferior vena cava, the catheter having passed through the ductus venosus. On some occasions, however it presumably lay within the portal vein. A continuous pressure record was taken from the catheter lumen using an inductance transducer (Elema) from which respiration rate could be counted, although not necessarily at all times, as physical activity of the baby caused disturbances. The minute to minute activity of the baby was observed by one of us and was recorded as one of four grades.[1] This visual assessment was later cross-checked with disturbances on the ECG and pressure traces.

Material

Ten babies (two female and eight male) ranging in weight from 1.97 to 4.16 kg and from to 8 days of age were studied. One infant (B) had a birth weight less than 2.5 kg.

[1] 0 (sleep), 1 (movement in one limb, infant asleep or no movement but infant awake), 2 (movement in 2 or more limbs, infant asleep or awake), 3 (all limbs moving and the baby crying).

Six infants (A, B, C, D, F, I) had been transferred from maternity hospitals for observation because of heart murmurs (four), fever of undetermined origin (one) and prematurity with transient postnatal asphyxia (one). In each the physical examination, pertinent laboratory studies and hospital course were entirely normal. Three infants, (E, H, J) had hemolytic disease of the newborn due either to Rh (E) or ABO incompatibility (H, J). Exchange transfusion had previously been performed in two (E, J). One infant (G) had hyperbilirubinaemia of unknown cause. In none of the latter four infants did the indirect serum bilirubin concentration rise above 20 mg/100 ml and the neurological examination and hospital course of each was entirely normal.

Procedure

After having been fed between 8 and 9 a.m. the various connections were made and the infant was placed inside the incubator hood and recordings begun, the procedure taking between 30 and 60 min. The room was darkened and noise minimized from then on. The temperature within the hood was maintained between 31 and 34°C with two exceptions (C, H). In the former the temperature rose steadily from 31 to 36°C, in the latter the temperature was maintained between 29–30°C.

A continuous infusion of 3.0 dextrose in 0.45% NaCl was maintained at a low rate (0.19 ml/min) to prevent clotting within the catheter. When stable conditions were achieved, usually about 40 minutes after the catheter was inserted and the baby was asleep, the dextrose–saline infusion rate was increased to 0.43 ml/min for 10–15 min, followed by the NAd, solution 0.2 to 1.0 μg/kg/min, in volume 0.43 ml/min (but occasionally 0.19 ml/min). The NAd infusion was usually bracketed between dextrose–saline infusions. The total volume of fluid infused was between 12 and 20 ml/kg over the whole test period. The test was terminated within 5 hours of the previous feed in all cases. No untoward reactions during or

TABLE 1 *Synop*[illegible]

During control periods O_2 consumption and CO_2 output are the means of steady state levels [illegible] are the peak values btained *during or immediately after the infusion. The pulse rates correspond* details) Hood temperature is the environmental temperature of the baby above knee level.
The percentage peak metabolic response was calculated as the percentage hange of the mean [illegible] post-control period, see F H, I)

					Pre-control period										
					Time					Temperatures			Dose μg/kg/min	Time	
Baby	Sex	Birth wt(g)	Age (days)	Study wt(g)	Start	Stop	O_2 ml/min	CO_2 ml/min	Pulse/min	Rectal	Skin	Hood		Start	Stop
A	M	[illegible]800	8	3570	28	57	22.8	20.8	128	36.6	33.8	32.4	0.2	[illegible]	[illegible]
					86	111	24 1	21 6	128	36.3	33.6	32.7	1.0	112	[illegible]
B	M	2050	4	2380	57	100	12.9	10.9	128	36.2	32.0	32.4	1.0	100	[illegible]
C	M	2310	3	1970	40	64	12.0	9.4	1[illegible]4	34.6	30.5	34.8	0.4	[illegible]	[illegible]
D	M	2960	4	2580	61	84	16.0	11 7	136	36.[illegible]	34.1	32.8	0.4	[illegible]	[illegible]
					103	147	17 1	12.2	140	36.5	34.5	33.[illegible]	0.4	[illegible]	[illegible]
E	M	3750	3	3510	26	93	21 6	16.2	116	35.8	30.9	32.3	0.4	[illegible]	[illegible]
F	M	3490	7	3090	60	85	20.7	14.[illegible]	115	35.2	29.2	32.6	0.4	[illegible]	[illegible]
													0.[illegible]	111	[illegible]
					111	136	22.0	17 0	134	35.3	30.0	32.0	0.4	[illegible]	[illegible]
					139	158	21.6	18.0	130	34.5	29.5	31 4	0.4	[illegible]	[illegible]
G	F	3620	6	3160	20	47	[illegible]1.6	19 0	1[illegible]0	36.8	[illegible]8.1	30.5	0.4	91	[illegible]
					148	168	21 6	17.[illegible]	134	37 1	28.8	31.0	0.8	[illegible]	[illegible]
H	F	3430	8	3100	18	40	20.8	[illegible]0.4	126	36.4	28.4	29.3	0.4	[illegible]	[illegible]
					63	83	21.5	16.6	130	37 0	27.8	30.5	0.6	[illegible]	[illegible]
I	M	3250	2	2960	43	70	[illegible]1 4	19.1	88	37 1	[illegible]8.6	31.2	0.4	[illegible]	[illegible]
					120	156	22.9	18 6	110	36.9	28.0	31.8	0.2	157	[illegible]
	M	4690	6	4160	63	87	[illegible]3.2	23.6	116	36.7	[illegible]7 4	30.8	0.2	[illegible]	[illegible]

after the test were observed except for tran sient bradycardia in some instances in the early stages of NAd infusion.

Results

The results are summarized in Table I There was a clear indication that respira tory metabolism increased in all babies[1] ranging for oxygen consumption from 13 % to 101 . A dose of 0 2 μg/kg/min evoked a definite metabolic increase in one infant otherwise the smallest effective dose was 0 4 μg/kg/min

In one infant (I) a noradrenaline dose of 0.2 μg/kg/min resulted in slight arousal *without metabolic response* At a dose of 0 4 μg/kg/min the arousal was more pro nounced and was associated *with* a meta bolic response

A moderate tachycardia was observed

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[1] Infant A had no metabolic, cardio-vascular or central nervous system response t either 0.2 or 1 0 μg/kg/min. At the conclusion of the study *it was discovered that the catheter* although in the umbilical vein, was not well secured and the umbilical dressing was soaking wet Presumably the infant received *little if any* noradrenaline The study was nonetheless useful because it demonstrated that steady st t could be main tained for long periods, in this *instance* 169 minutes.

/ results

(during dextrose-saline infusion) during an interval ranging from 6 t 20 min. During NAd these values
le same periods as the gas analyses. Temperatures are the mean values for each period (see text for

le pre and post-control periods (or from the pre-control period only when there was no satisfactory

Noradrenaline infusion period											Post-control period					
O_2 ml/min (peak)	CO_2	Pulse/ min (peak)	Temperatures			Arousal	Peak met. % control		Time		O	CO	Pulse/ min (peak)	Temperatures		
			Rectal	Skin	Hood		O_2	CO	Start	Stop	ml/min (peak)			Rectal	Skin	Hood
1.9	18.9	120	36.7	34.7	33.2	0	−9	−11	98	111	24.1	21.6	128	36.2	33.6	32.
2.8	21.0	126	36.2	33.3	32.5	0	−1	+2	130	108	22.4	19.4	124	36.3	31.5	32.9
7.2	14.6	—	36.4	34.3	32.7	±	+20	+35	115	149	14.7	11.1	140	36.8	34.7	32.4
6.1	11.7	140	36.1	33.8	33.6	0	+18	+21	89	122	12.7	10.0	148	35.7	34.5	36.1
2.8	17.2	180	36.4	33.9	32.8	+ + +	+37	+43	102	147	17 1	12.3	140	36.6	34.5	33.3
1.8	16.9	170	36.6	35.4	33.5	+ +	+25	+23	162	163	17 4	12.8	164	36.6	34.0	33.5
28.3	35.1	156	—	32.2	33.4	0	+60	+69	137	164	23.8	19.0	140	36.4	33.3	33.
30.0	23.3	174	35.3	30.0	32.7	+ +	+35	+64	—	—	—	—	—	—	—	—
20.9	17.0	124	35.3	30.0	32.2	0	+6	+20								
23.5	28.1	184	35.0	28.8	31 4	+ + +	+54	+61	129	158	21.8	18.0	120	34.5	30.5	31 4
23.3	22 4	180	35.0	29.2	—	+ + +	+31	+23	161	190	21.3	16.8	116	34.8	28 9	31.3
4.0	21.7	110	36.9	28.0	31.1	0	+11	+20	148	158	21 6	17.3	124	37 1	29.5	31.0
7.4	21.8	168	37.1	28.6	31.1	0	+"6	+19	165	190	22.0	19 1	148	37 1	30.1	31.4
23.3	24.3	173	36.9	27.9	29.6	+ +	+23	+31	63	83	21.5	16.6	130	37.0	27.5	29.5
33.2	30.3	184	36.9	28.0	30.1	+ + +	+101	+136	—	—	—	—		—	—	—
28.3	28.3	126	37.1	28.8	31.5	+ +	+27	+35	120	186	22.9	19.6	110	36.9	28.0	31.8
23.4	18.4	110	36.9	27 4	31.8	+	+2	−1	—	—	—	—	—	—	—	—
28.2	30.5	150	36.7	27.2	30.9	±	+28	+31	103	134	28.2	22.8	124	36.9	25.7	31.0

whenever there was a metabolic response Prior to this in four babies there was a transient bradycardia the nadir occurring 4–6 min after the beginning of noradrenaline infusion. The heart rate declined 44 beats per min in two infants (B 1.0 μg/kg/min, and E, 0.4 μg/kg/min); in the other two infants, C and G the falls were 32 and 18 per min, respectively

In four infants the metabolic response was accompanied by arousal and increased physical activity In the five remaining infants there was either no appreciable activity (three babies) or this was, at best equi ocal (two) One example of each type of response is shown in Figs. 1 and 2.

Fig 1 illustrates the responses of a 7 day-old male baby of 3090 g (baby F) to repeated infusions of 0.2 nd 0.4 μg/NAd/kg/min. As far as our observations were concerned 0.2 μg NAd was subthreshold. The response to 0.4 μg NAd was consistently tachycardia, arousal and metabolic increase in that order The timing of the events is important and each of the responses to the three infusions of 0.4 μg/kg/min will be considered in detail. On the first occasion (90 min) the catheter was full of dextrose-saline and 1½ min

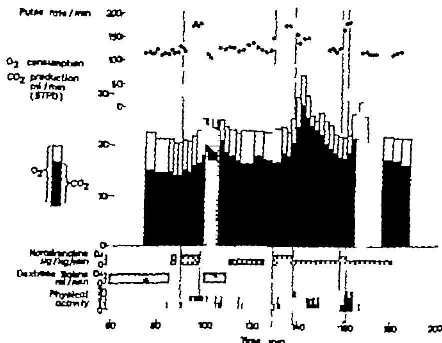


Fig 1 Responses of 7-day-old baby (F) to intravenous infusions of noradrenaline (0.2 and 0.4 µg/kg/min) and of dextrose-saline From above downwards are shown pulse rate respiratory metabolism, infusion, physical activity and time

The pulse rate/min was computed from the time taken for 40 beats. The vertical blocks indicate by their widths the time during which metabolism was measured and by their heights the O_2 consumption (open and shaded limits) and CO_2 production (shaded limits). The infusions are shown as dotted or grey horizontal bars, the former gives the duration and dosage of noradrenaline (NAd) and the latter the duration and flow of hypotonic dextrose-saline. Vertical guide lines run up at the start and finish of each infusion of 0.4 µg/kg/min NAd.

should be allowed for this to have cleared before NAd began to enter the circulation. Subtracting this from the delays observed in each response there was a lag of approximately 1 min before the heart rate began to rise 2 min before arousal appeared and 3½ min before metabolism began to rise (taking into account the lag time of the apparatus) On the second occasion (129 min) the catheter was full of a more dilute NAd solution (half strength for the preceding 0.2 µg/kg/min) and the delays (subtracting 1½ min for catheter clearance) were ½ min 2 to 3 min and 4 min for tachycardia arousal and metabolic increase respectively On the third occasion (158 min) the catheter was already full of NAd at full strength and the delays, with no catheter allowance this time were ½ min 1½ min and 3 min respectively In this baby we could not distinguish the cause of the metabolic response that is to say how much of it was an immediate result of increased muscular activity

In contrast the response of a 3-day-old male baby (E) of 3510 g whose activity during NAd was unchanged is shown in Fig 2. Noradrenaline at 0.4 µg/kg/min

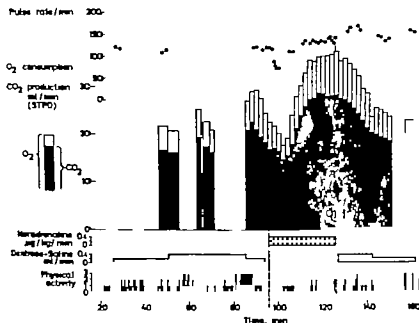


Fig. 2. Responses of 3-day-old baby (E) to intravenous infusions of noradrenaline (0·4 µg/kg/min) and of dextrose saline. From above downwards are shown pulse rate, O_2 consumption and CO_2 production, infusion, physical activity and time. Symbols as in Fig. 1.

had a pronounced thermogenic effect, preceded by transient bradycardia. The lowest heart rate occurred 3 min after the start of the infusion of NAd. About 1½ min of this delay can be accounted for by the catheter dead space so that the heart began to slow some ½–1 min after the NAd began to enter the circulation. The bradycardia lasted for about 7 min, during which time respiratory metabolism actually fell to below control values; the low points of both heart rate and metabolism were almost simultaneous if allowance is made for the time lag of the gas analyser. The subsequent metaboli response was clear cut, an increase of 60 % being achieved with no change in visible physical activity and maintained for 18 min, decreasing only when NAd was stopped. During the control period beforehand, while dextrose–saline was being infused, a 7 min period of considerable restlessness occurred spontaneously. This caused a 33 % peak increase in metabolism and throws into sharp relief the subsequent thermogenic response to NAd of double this amount which was ttained while the baby was almost completely t rest.

Changes in the respiratory quotient of more than 0·04 were seen in only three infants. The increased RQ during NAd infusion in two of them (F H) was possibly a result of hyperventilation.

Respiratory rates were rather erratic but in each instance rose when there was a metabolic response. The largest increase was 34 per minute from 44 to 78 during NAd infusion. No changes in rectal tem-

perature which could clearly be ascribed to NAd were noted. The failure to observe an increase in rectal temperature along with an increase in metabolism is doubtless due to the short observation periods to the relatively small increases in metabolism and the fact that increments of change less than 0 1 C could not be recorded. Skin temperatures were also constant with three exceptions (D E J) in each of whom there was a distinct drop (0 4 – 1 6 C) in skin temperature 7 to 11 minutes after the noradrenaline infusion began. This was followed by a return to previous values either while the noradrenaline was still being infused or during the following control period. Its explanation is not clear

Discussion

Noradrenaline in the dosage used, i.e. 0.2 to 1 0 μg/kg/min, caused the respiratory metabolism to rise In four of nine babies this was associated with an increased physical activity The means whereby the increased heat production was achieved is not certain but clearly the additional overt physical activity was not able to account for all of it. This was evident in the five babies who had a rise in gaseous metabolism but whose activity was unaffected, as well as in three of the active infants whose rise in metabolism seemed to precede the activity

There was no obvious shivering as judged either by direct observation or by ECG disturbance but increase in general muscle tone could possibly have gone unnoticed. Non-shivering thermogenesis is a distinct possibility this has been shown in the cold-adapted rat [6 7 12] The thermogenic properties of NAd which have been reported by Moore and Moore & Underwood [13 14] in the unanesthetized kitten and by Baum, Moore & Underwood [3] in the adult rat after dibenzyline treatment may be in the same category It appears unlikely that glucose and lactate (the products of glycolysis) are the responsible stimulants, since these vary independently of oxygen consumption in kittens and adult rats [2], even though catecholamines by their effect in activating glycogen phosphorylase [19] are probably important in providing supplies of fuel.

A striking feature of the arousal which occurred during NAd infusion was the abruptness with which it began and, particularly ceased (Fig 1) leaving no doubt that its genesis was NAd. The arousal and crying as well as increasing heat production by physical effort on the baby's part could have the teleological effect of drawing the mother's attention to a situation requiring her action to furnish a warmer environment Experimental evidence concerning the arousal response to blood borne catecholamines particularly adrenaline has been discussed by Dell [5].

Cardiovascular changes were not followed in sufficient detail to allow firm conclusions to be drawn. Because blood pressure was not measured its changes can only be inferred. The bradycardia seen in four of nine infants was presumably the result of a baroceptor reflex. Whether or not the hypertension persisted we do not know but the heart rate certainly recovered and then rose with continued infusion of NAd. The hold-up of metabolic response during bradycardia could be due to a limitation of cardiac output If the bradycardia is of baroceptor reflex origin, as is claimed in the adult [8], then one

could readily visualize a temporary slowing of the circulation which would explain the transitory reduction in respiratory meta bolism seen during the period of brady cardia in these infants (see Fig * 103–106 min) It is also possible that the cardio-vascular receptor sites are more avid for circulating NAd, but that they saturate rapidly after which a metabolic threshold concentration is able to be achieved in the blood. In favor of this was the observa tion that in all the babies the heart rate was the first of the observed phenomena to alter Once NAd had cleared the catheter a change was seen in about 1 min, and this can be seen in Fig 1 (F) where the response to NAd was a tachycardia. Although a good deal is known bout the cardiovascular *responses of the adult man* to catecholamines, only little is known about those of the baby [1] The pharmacology of the catecholamines in the neonatal period may have its own individuality particularly in respect of accessibility to receptors.

The following tentative scheme is sug gested to account for the changes observed in the babies in this study NAd in the blood is competed for by several receptor sites including cardiovascular metabolic and central nervous. The relative sensiti-vity of these sites to NAd and the dose administered determines the type of res-ponse *which can be a mixture of all three* The metabolic response of babies ppears to be either a direct action on a biochemi cally sensitive system lone or this plus a direct and indirect ction on the central nervous system producing rousal nd possibly other effect On thi basis one could visualize that a baby I receipt of a cold stimulus could liberat NAd and thereby produce extra heat for the main-tenance of thermal balance

However before one could accept this hypothesis much additional evidence is required and further work is in progress to this end Particularly do we need to know whether an increased secretion of NAd occurs at lower environmental tempera tures Suggestive evidence that this might be the case comes from the increase in vanillyl mandelic acid (VMA) excretion in newborn babies in the "cold" A 25 % in crease in urinary excretion rate at an en-vironmental temperature of 75 F (23.9°C) as compared with 85 F (29.4°C) of this known metabolit of adrenaline and nor adrenaline wa demonstrated in babies 4–9 days of age [18]. Because VMA can be *produced from ither* NAd or Ad, the source cannot however be specified.

Summary

1 Nine newly born infants were given NAd by continuous intravenous infusion at a dose rat of 0.2 to 1.0 μg/kg/min for short periods.

2 All infants responded with an in crease of respiratory metabolism. In four infants the metabolic response was c companied by arousal and increased physical ctivity but in five it occurred *without ppreciable change in ctivity* A tenth infant for technical reasons, l most certainly received little if any NAd nd did not respond

3 A formulation of temperature control in the newborn is presented which sug gests that NAd could be the mediator of a n mber of integrated thermoregulatory responses.

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Pediatric Clinic
Karolinska Sjukhuset
Stockholm 60
Sweden.

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From the Pediatric Clinic of Athens University Athens, Greece

Serum Transaminases in Diphtheritic Myocarditis

Their Relation to Electrocardiographic Findings

by C. CHOREMIS and J LEONIDAS

Recently the development and wide spread application of methods of quantitating levels of enzyme activities in the blood or serum in man has resulted in a significant advance in the diagnosis of heart disease [1 9 13 15]. The more valuable enzyme systems, in this regard, are the transaminases (glutamic-oxalacetic (SGOT) and glutamic-pyruvic transaminase (SGPT)) and lactic dehydrogenase It has been shown that an increase in the serum level of these enzymes is a valuable laboratory indicator of acute myocardial damage [1 13 15]. High rates of SGOT have been obtained in a good number of cases with rheumatic carditis [16] and in a few patients with diphtheritic myocarditis [5]. Serum glutamic pyruvic transaminase is not a sensitive index of cardiac muscle damage however it was found to be increased in cases of heart disease with extensive myocardial necrosis or marked congestion of the liver due to right-sided heart failure [18 20 21]

It is well known that the most serious complications of diphtheria are mainly cardiac involvement and secondly the infection of the nervous system In regard with the former post mortem examinations reveal evidence of parenchymatous myocarditis sometimes interstitial changes and areas of nearly complete necrosis particularly in severe forms of diphtheritic myocarditis [7 8 17]

It is true that diphtheria has become a rare disease in many countries Unfortunately in Greece the disease exists in an endemic form We had the opportunity of studying the transaminase activity in cases of malignant diphtheria with cardiac involvement in correlation with ECG control during an outbreak of the disease last autumn and winter

Material and Method

Our material consists of 49 cases of diphtheria admitted to the Infectious Disease Department of the Children Hospital of Athens University Their ages range from 1½ to 12 years. Twenty patients out of this number did not show any clinical or ECG evidence of myocarditis during their hospitalization. These were considered as controls in our study (Group I). From the remainder 19 patients formed a separate group (Group II), because on admission they had the malignant form of diphtheria All these patients had ECG evidence of myocarditis Finally in the last group (Group III) are included 5 patients who were referred to [illegible] long after the myocarditis had been established ([illegible] group IIIa) and 6 more patients in whom the ECGs displayed on

admission signs of incomplete right bundle-branch block, which persisted during hospitalization and thereafter (Sub-group III*b*)

A 12 lead ECG was taken by a direct recording machine in every patient, at frequent intervals, depending on the severity of the case The minimum number of ECGs was three to five· however several tracings were recorded, often during the same day in severe cases, with a total number up to 25.

The degree of ECG abnormality was graded from 1 to 4 according to Boyer & Weinstein s classification slightly modified [4] Grade 1 variation consisted of slight alterations in the ST segment or T wave. Grade 2 changes were either more marked Grade 1 changes or prolongat ons of PR or QT intervals. Grade 3 was made up of records showing a combination of Grade 2 changes with more intense ST segment and T wave abnormalities. Finally Grade 4 was reserved for cases characterized by disturbances of impulse formation and/or conduction (supraventricular tachycardia, ventricular tachycardia, nodal rhythm, complete or incomplete A–V dissociation or block, bundle-branch block) or very marked aberrations of the ST segment or T waves.

It is worth mentioning that several, or all, of these ECG abnormalities were simultaneously observed in the same tracing or appeared in successive records on the same patient.

Serum transaminase activities were determined spectrophotometrically according to Karmen's method [9], in which the following normal ranges are adopted SGOT 10–40 units/ml/min, with a mean value of 22.1 and S D $\pm$ 6 8 units; SGPT 5–35 units/ml/min, with a mean value of 16 and S.D $\pm$ 9

Serial serum enzymatic estimations were performed in Group II and III depending on the clinical course and ECG abnormalities, while the number of enzymatic determinations were less in the patient of Group I

Results

Tables 1 ° and 3 show the results obtained during a serial testing of SGOT and SGPT in all three groups of patients, respectively

Group I (control) is characterized by a lack of ECG abnormalities on repeated tracings and serum enzyme activity was proved to be within normal limits on repeated determinations (SGOT levels ranged from 11 to 37 4 units/ml/min and SGPT from 5 to 23 7 units)

Group II is characterized by varying degrees of ECG changes indicative of myocardial involvement. All nineteen patients of this group were found to have increased SGOT activity Six patients out of nineteen died with markedly elevated enzymatic values, in four of the fatal cases there was a progressive rise in SGOT levels up to the moment of exitus while in the remaining two a slight decline of the enzymatic activity was noted prior to the occurrence of death following a progressive elevation. The highest value in this group was 441 units/min in Case 11 while three other patients had values above 200 unit (Cases 6 15 and 17) In one of the recov erers serum enzymatic activity returned to normal levels almost simultaneously with the subsidence of ECG abnormalities and in the remaining 1_ patients the ECG continued to display abnormal patterns for a long time varying with each case after the SGOT activity had returned to normal levels. The highest value of SGOT in this group of survivors was 19? unit ml/min. The duration of elevated SGOT activity ranged from 1 to 18 days.

Group III has been divided into t o subgroups (III*a* and III*b*). In patients of Sub-group III*a* SGOT activity was found to be normal or slightly elevated. Sub-group III*b* patients with ECG evidence of incomplete right bundle-branch

TABLE 1 *Group I SGOT and SGPT levels in 20 patients with diphtheria but without clinical and/or ECG evidence of myocarditis*

Case	Sex	Age, years	Day of illness	SGOT unit /ml/min	SGPT unit /ml/min
1	F	9	8	+–	16.5
2	F	11	7	1	14.5
3	M	4	6	19	8.3
4	M	4	8	16	12
5	F	4	6	30.5	8.6
			13	1.5	1
6	F	3	6	8.5	11
			9	2	14.6
			15	40	18.9
7	M	6	3	15	6
			9	3 4	1
			14	11	8.5
8	M	5	7	1 6	8.5
9	M	2	6	18 2	6.8
			9	4	6.5
10	M	4	4	23	7.5
			9	16	7.5
11	F	4	6	1 3	.5
			13	21 4	11
12	F	7	5	19 6	1
			10	46	14.3
13	M	7	5	14.9	9 3
			7	16.5	10.6
			11	4.3	5 5
14	F		5	18.6	1 3
			8	16_	8.4
15	M	3	5	23	5 5
			8	18	9 4
16	M	2	7	18	11
			11	19	10 5
			21	19	5
17	F	11	4	4	11 4
			9	28	8_
18	F	12	5	30	1
			10	18.5	8
19	F	8	4	32.5	21.7
			14	35	19
			24	46.8	1.5
20	F	10	4	32	16.4

block showed invariably normal SGOT values.

As far as SGPT activity is concerned, it was found that only Group II included patient with abnormal values. As a matter of fact the fatal cases showed moderately increased serum levels with one exception (220 unit /ml/min in Case 11) while among the remaining patients SGPT activity was found to be slightly elevated in four with moderate rise in two of them (Cases 14 and 18). Finally there were seven patients in this group with no demonstrable SGPT elevation.

The following case reports pertaining to Group II illustrate two of the patterns of the serum enzyme alterations and ECG changes which we have found in diphtheritic myocarditis

TABLE 2 *Group II Serial SGOT and SGPT determinations in 19 patients with malignant diphtheria and myocarditis*

Case	Initial	Sex	Age years	Day of illness	SGOT units/ml/min	SGPT units/ml/min	ECG gradation	Outcome
1	S. D	M	3.5	4	1_5	8	1	
				7	19	10	—	
				11	75	1	2	
				12	22.5	18	—	
				13	_5	19	**	Recovery
2	G M.	M	8	2	24	11.5	1	
				4	55	17	**	
				5	93	*0.5	—	
				6	58	25		
				8	76	30	3	
				11	49	30	—	
				15	45	35	2	
				20	31	26	**	Recovery
3	J S.	M	7	10	186	*9	** 4	
				11	155.4	23	2* 4	
				12	125.4	25	4	
				14	95	28.5	** 4	
				15	63	26	—	
				18	22.4	19	—	
				25	*6	1	4	Recovery
4	P A.	M	8	14	51	17.5	1 4	
				13	40	13	1 4	
				16	*8	10.2	1 4	
				*0	4.3	11	1 4	Recovery
5	M. A.	F	6	4	35.5	30	1	
				5	32	30		
				7	50.5	34	3	
				8	105	41 4	3*	
				9	86	38	—	
				10	94	36.5	3	
				11	77	3_	3	
				13	48	36.2	3	
				15	29.2	**	**	Recovery
6	A. T	F	4	6	81	4	4	
					0	15	4	
				8	40	16		
				1	33	10.8	1	Recovery
7	A. K.	F	10	9	103	45.8	3 4	
				10	110	36.7	3 4	
				11	147	58	3* 4	Death
8	J M.	M	8	11	109.5	48_	4	
				21	82.2	41	**	
				*6	38	34		Recovery
9	T C.	M	6	5	295	82	4	Death
10	B. A.	F	8	6	115	45.6	4	Death
11	M. A.	F	6	10	157	30.9	4	
				11	*71	37.8	** 4	
				1	*61	33.3	4	
				13	301	64	3 4	
				15	441	220	4	Death
1	P M.	F	4	4	20.5	12	Normal	
				6	144	31	—	
				7	106	39.5	1	
				9	43	23.5	2	

Table II *(cont.)*

Case	Initial	Sex	Age, years	Day of illness	SGOT units/ml/min	SGPT units/ml/min	ECG gradation	Outcome
				14	[illegible]9	23	1	
				19	26.5	20.5	1	Recovery
13	M.C.	F	6	5	[illegible]8.5	16	Normal	
				9	104	39.2		
				10	132	4[illegible]2		
				11	68	40.5	1	
				1	41	18	1	
				25	40.5	[illegible]7.5	1	
				30	26[illegible]	10 3	1	Recovery
14	K.T.	M	6	4	18 4	10 9	Normal	
				5	19.6	11 3	1	
				6	165.6	39 5	2	
				7	192	44	4	
				8	172.6	49	4	
				9	104	5[illegible]5	4	
				11	98.2	60.1	3	
				13	67	59.4	—	
				15	73	50[illegible]	3	
				23	44	36	3	
				30	29.3	1[illegible].5	1	
				62	76.4	10.8	Normal	Recovery
15	J.A.	M	8	4	50.2	10	4	
				9	182	31	4	
				10	295	69	4	
				12	274.9	—	4	Death
16	E.I.	F	7	4	35.5	9 5	1	
				7	111	23.5	1 4	
				11	61	28	2	
				15	32	17		
				20	1	18.5	1	Recovery
17	G.K.	M	8	4	36.4	11.5	—	
				7	350	48	4	
				11	183	69	4	Death
18	C.B.	F	5	5	36	19.5	Normal	
				7	58	4		
				12	122.6	9	2 4	
				16	63.5	60[illegible]	[illegible] 4	
				19	29.9	31 4	2 4	
				29	10.4	12	1	Recovery
19	D.G.	F	4	5	42	[illegible]9 4	1	
				9	36.1	14.2	Normal	Recovery

Case 11. M. H., a 6-year-old girl was admitted t the hospital on the 9th day of her illness with diagnosis of faucial diphtheria. Despit treatment the patient showed clinical signs of myocarditis and abnormal ECG findings 4 days prior to her admission, because of which she was referred to us. Physical examination revealed a pale-looking girl with a tachycardia, weak heart sounds, gallop rhythm and low blood pressure (3 40). An ECG (Fig 1) displayed signs of 1st degree A V block with S–A tachycardia (grade 2 changes), complet right bundle branch block alternating at times with in complet left bundle-branch block and marked degree of subendocardial ischemia and injury (Grade 4 changes). The patient condition gradually deteriorated and she died on the 15th day of her illness with mild signs of right-sided heart failure Serial

TABLE 3 *Group III*

Case	Initial	Sex	Age, years	Day of illness	SGOT units/ml/min	SGPT units/ml/min	ECG gradation	Outcome
Subgroup III a. Late serum enzyme determinations in 5 patients with diphtheritic myocarditis								
1	D S	M	6	15	49	30	2 4	
				16	35	22	—	
				21	40	20	—	
				23	28	24	2	
				30	22	15.5	1	Recovery
2	G. S.	F	12	17	43	10	2	
				19	40	13		
				23	38	14.2	2*	
				30	33.5	13	1	Recovery
3	M. A.	F	10	21	35	15	1	
				23	29	16	1	
				31	16	11.4	1	Recovery
4	A. A.	M	7	17	44.1	29	3	
				19	26.3	19	1	
				23	23	22	1	Recovery
5	E. T	F	7	33	21	17	1	
				34	7	5	1	Recovery
Subgroup III b Serum enzyme determinations in 5 patients with diphtheria and incomplete right bundle-branch block.								
1	A. A.	F	9	4	30.4	15.3		
				14	21	13.2		Recovery
2	M. M.	F	13	5	29.4	1		
				13	31	16.5		Recovery
3	T D	M	7	4	19	10.6		
				14	1	6		Recovery
4	S. S.	F	5	6	26	18		
				9	19	11		Recovery
5	C. F	F	3.5	2	10.5	8.3		
				15	18	8.9		Recovery

SGOT and SGPT activity determinations are shown in Fig 2. Note the progressive elevation of serum enzyme levels. An ECG taken prior to her death showed complete *A–V block (Grade 4 changes).*

Case 16 H. I a 7 year-old girl, who was admitted to the hospital on the 4th day of her illness with clinical signs of malignant diphtheria. Figs. 3 and 4 show the ECG findings and the serum enzyme alterations during hospitalization. As a matter of fact on admission the ECG (A, A') was borderline and the serum transaminases within normal limits. On the 8th day the ECG (B B') displayed Grade 1 (ST segment changes) and Grade 4 changes, while SGOT rose up to 111 unit /ml/min. On the 12th day the ECG (C C') revealed Grade ST segment and T wave changes associated with a decline in SGOT level (61 units/ml/min) the latter returned to normal on the 15th day while *the ECG abnormalities (D D') persisted* longer (Grade changes on the 22nd day). The ECG (E, E') was within normal limit on the 34th day

Discussion

As is indicated in Table 1 we were not able to detect any abnormal elevation of serum transaminase in all twenty patients in whom there was no clinical or ECG evidence of myocarditis. On the contrary

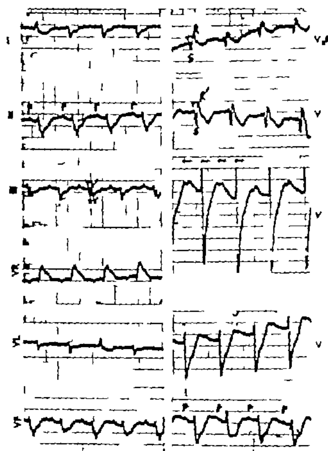
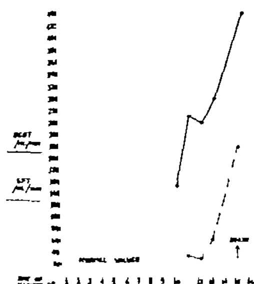


Fig 1 Electrocardiographic findings in patien M. H (Case 1)

Table 2 illustrates very striking alterations in the activity of the enzyme systems which deserve a detailed analysis. It was known from previous studies [4 6, 7 8 10], as well as from a recent one at this hospital [3] concerning a large number of cases of diphtheria (500) that ECG evidence of myocarditi usually appears at the end of the 1st week d ring the 2nd week and very occasionally later W have observed in our patients (Group II) that elevation of serum enzyme activity roughly coincides with the onset of ECG hanges This could be easily explained on the bas that both ECG findings and serum enzymatic alterations are a manifestation of acute cellular damage which occurs during the early stage of myocarditis [11 13] Unlike myocardial infarction, the elevation of serum enzyme activity lasted longer in most of our cases of diphtheritic myocarditis (up to 16 days) This again can be explained rationally when one considers th mechanism of production of the tissue damage In myocardial infarction the causative factor (coronary occl sion) act n a sudden way nd the release of the enzyme from the damaged myocardial


Fig. 2. Serial determination of SGOT and SGPT activity in patient M. H. (Case 11).

cells does not last more than a few days unless a new process takes place [2, 13]. On the contrary, the diphtheritic toxin acts longer on the heart muscle and therefore the release of the enzyme is more prolonged. Another point to be emphasized is our observation that the highest value of enzyme obtained in this series was 441 units, which is much less than the highest reported for myocardial infarction [13]. Perhaps in myocardial infarction the occurrence of massive necrosis of heart muscle in some cases is responsible for these high values in contrast to diphtheritic myocarditis, where rather smaller and scattered areas of necrosis take place [3, 8], so that the overall amount of the necrosed myocardium is less than in myocardial infarction. Comparing the behaviour of the two transaminases in diphtheritic myocarditis, we have observed that abnormally elevated SGOT levels were much higher and they constituted a more constant finding than the respective SGPT levels in the same patient, as in myocardial infarction [13, 21].

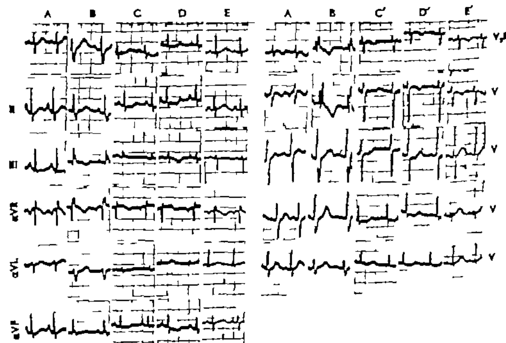


Fig. 3. Electrocardiographic findings in patient A. M. (Case 17).

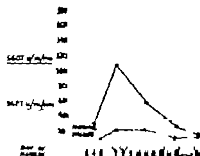


Fig. 4 Serial determination of SGOT and SGPT activity in patient A. M. (Case 17).

However we think that elevated SGPT levels in diphtheritic myocarditis may accompany relatively lower increase of SGOT activity than in myocardial infarction, so that the margin between the two enzymes is usually smaller in the former than in the latter It is noteworthy also that the ECG abnormalities in all our cases but one persisted for a long time after the SGOT activity had returned to normal levels, depending on the severity of the cardiac muscle injury This is due to the development of myocardial fibrosis, as in myocardial infarction

It has been well established that acute heart muscle damage is not usually accompanied by high SGPT titers The most obvious explanation is that myocardial cells are rich in GOT but do not contain significant quantities of GPT The latter is abundant in liver cells [20] High SGPT levels in myocardial infarction have been found in very xtensive cardiac muscle necrosis or in cases complicated by congestive heart failure with centrilobular cell necrosis [13] In our cases of diphtheritic myocarditis SGPT wa moderately elevated in severe cardia involvement usually complicated by passive congestion of the liver

SGOT determinations may be of value in those cases of diphtheritic myocarditis where the ECG shows conduction disturbances, which may mask the ECG manifestation of the acute phase of diphtheritic myocarditis, whenever these arrhythmias precede the diphtheritic infection.

As far as the prognostic value of the serum enzyme activity is concerned, the following should be taken into consideration.

(a) High titers of SGOT activity imply a guarded prognosis. A rapidly progressive rise of the serum enzyme level exceeding that of 200 units/ml/min is a sign of poor prognosis

(b) A progressive increase in SGOT activity followed by a gradual decline is suggestive of a good prognosis unless serious disturbances of conduction persist (A–V block)

(c) Increased SGPT values accompanying elevated SGOT levels also denote a guarded prognosis.

Conclusions nd Summary

Forty nine cases of diphtheria were studied from an enzymatic (SGOT and SGPT) point of view during n outbreak of the disease in correlation with ECG control It ha been shown that serum enzym determinations mak valuable laboratory indicator of cute myocardial injury due to the action of diphtheritic t xin The behavior of the enzymati tivity curve in diphtheritic myocarditis differs from that seen in myocardial infarction in that the duration is usually longer and the height is less in th former

than in the latter SGOT estimation is a good diagnostic and prognostic aid in diphtheritic myocarditis and it can be considered as an adjunct to the ECG diagnosis of the disease the former being on certain occasions superior to the latter.

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Pediatric Clinic
St Sophia Children Hospital
Athens
Greece

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From the Pediatric Department (Head Prof. P. Plum) of the University Hospital, Copenhagen

Prognosis in Meningitis Neonatorum

by HOLGER DYGGVE

Despite the use of antibiotics the prognosis in neonatal meningitis is poor. This is primarily due to the fact that the initial symptoms are vague and thus the diagnosis is often delayed. Furthermore, the disease is usually caused by *E. coli* or coliform bacteria, which are often insensitive to antibiotics. These organisms are generally non-pathogenic in older age groups.

Although many small series of cases of neonatal meningitis giving immediate results have been reported, only a few larger series and follow-up studies have been published. The largest series due to *E. coli* is that of Mogensen *et al.* [12], comprising 23 cases from several pediatric departments in Denmark (1956). About half of the infants died during the neonatal period or soon after. Six survived with defects such as pareses or mental deficiency. Only six were completely cured, all of whom were born during the years 1931–1938. Only one infant from the period 1946–1950 survived, and this had a permanent defect. The authors found that delivery was difficult or complicated in about two-thirds of the cases.

The sources and routes of infection in neonatal *E. coli* meningitis have been investigated by Dupont & Thamdrup [ ] among others. In of 6 cases examined the infection originated from the mothers, since the same type of *E. coli* found in the infants was also isolated from the mothers' vagina or urine and feces. Among the seven strains of *E. coli* cultured from the cerebrospinal fluid, blood, nose etc. of the infants, none belonged to the special types known to cause infantile diarrhea.

The incidence of meningitis in the newborn is difficult to evaluate. According to Dupont & Thamdrup, it is estimated to be about 0.5 ‰. Among 160 cases collected from the literature, Flensborg [3] in 1943 found 50 % to be due to *E. coli* and coliform bacteria. Nine per cent of 409 cases of purulent meningitis from the Children's Hospital, Los Angeles, published by Esmond Smith [17] in 1954, occurred among infants less than one month old. The incidence was not as high in any other month of life. In only 19 of these 36 cases could the responsible bacteria be demonstrated, 13 being due to *E. coli* strains. Two-thirds of the 36 patients died. Nine of Dupont & Thamdrup's 11 cases in newborn infants (about 80 %) were due to *E. coli*. The frequency of *E. coli* infections among cases of neonatal meningitis seems to vary in different countries. Thus Debré *et al.* [1] had 5 cases caused by intestinal bacteria among a total of 12 cases. All these five infants died, whereas the remaining infants, with meningitis due to pneumococci and meningococci, survived. In Italy [20] only 2 of 15 cases were found to be due to *E. coli* infection, while 8 were caused by *M. pyogenes aureus*. From China [8] 2 cases of *E. coli* meningitis, 5 of meningococcal, 1 of pneumococcal, and 3 of unknown origin were reported in 1958.

Meningitis is more common among pre-

maturely born than full term infants [2, 3]. The diagnosis is especially difficult in prematures and, consequently the prognosis is very bad For example, in the series of Kagan *et al.* 11 of 1 infants died. In 9 of them the disease was due to *E coli* infection [6].

During the last decade increasing numbers of meningitis cases due to infection with *Listeria monocytogenes* have been reported, especially from Germany [16]. The first to report disease in man caused by this organism was Nyfeldt [13] in 1929 In newborn infants with Listeriosis a septicemic form with disseminated small granulomas in the organs is characteristic. At the State Serum Institute *in Copenhagen 10 cases of Listeriosis with* positive culture from the cerebro-spinal *fluid (CSF) were found during one year* (1958–59) During the same period *E coli* *was cultured from 19 of 1710 specimens* I CSF Three of 11 cases of Listeria meningitis *reported by Kristensen & Jensen [9] occurred* in newborn infants. Two of the three infants are included in the present report Two of the infants died while the third has hydrocephalus and mental retardation (see Case 18 below) Cases of Listeriosis in infants have also been reported, among others, by Hood [5], Luttor [10] and Welshimer & Winglewish [21]. Kaijser & Malmström Groth [7] have collected 13 cases of Listeriosis in newborn infants in Sweden. Only four of these infants survived, one with hydrocephalus.

Material

At the Pediatric Department of the Rigshospital in Copenhagen 19 infants with neonatal meningitis ha e been treated during 1950–1959 One add tional case from one of the obstetric departments was diagnosed post mortem, bringing the t tal to 20

Seasonal variation Five cases occurred during spring and summer while 15 cases were seen luring autumn and winter There wa a maximum of cases in January

Sex distribution. Si teen f the 20 cases (80%) occurred in males, seven of whom died. Five of these cases were *due to E col*

Etiology and mortality

Etiology	Number	Deaths	Percentage of deaths
E coli	8	4	50
Klebsiella	1	1	100
Listeria	2	1	50
Serous (virus?)	3	0	0
Purulent (no growth)	5	1	20
Purulent (No bact. exam.)	1	1	100
Total	20	8	40

or coliform bacteria (it is possible that all 7 cases were due to these organisms, since culture was not made in 1 case and only after long insufficient treatment with anti*biotics in another hospital in the other). Of* the four girls with meningitis one died (due to Listeria) The same high incidence of males was found by Randall [15], who had five boys among his 6 cases, and by Mogensen *et al.* [12], who had 16 boys and nine girls in their series. Meningitis (purulent as ell as serous) also prevailed among boys and men *in Gregersen s 736 cases [4], three-fifths being* males and two-fifths females. Six of Welshi*mer & Winglewish s 7 cases of Listeria me*ningitis occurred in males (f these were *neonatal cases and both died)* In the present series both the cases f Listeriosis were in girls. The reason why the disease is more common and the mortality higher in males than in females is unknown

Birth History

The finding that neonatal meningiti is very often seen in association with difficult and complicated deliveries was confirmed in this series. Seven infant were delivered by forceps or vacuum extractor two by cesarean section and four were breech presentations. One mother had pre-eclampsia, another anemia and a third complete placenta previa. One infant was one of twins. One mother had had two stillborn *infant and three early abortions,* in add tion t two normal chil*dren. She had a flat pelvis and was delivered* by cesarean section. Her child made *complete recovery from h serous meningi-*

tis. Another infant was delivered precipitously (½ hour). Premature rupture of membranes was observed in only 3 of 17 cases in which knowledge about this could be obtained. Only two mothers were febrile prepartum.

The mothers' age at delivery was not unusual: two were less than 20 years, eight between 30 and 34 years (only one of these mothers was primipara). One mother was 40 at delivery and primigravida. Eight mothers had had miscarriages (four of these more than one abortion). Fourteen of the 20 mothers were primiparae.

Infant at birth. Of the 20 cases only 5 were normal, uncomplicated, term deliveries. Seven infants had a birth weight below 2500 g. Thus, more than one-third of the infants were premature. Furthermore 11 had birth weights below 3000 g. Only two weighed more than 4000 g. Seven infants were asphyxiated at birth, one for more than 5 minutes. Five of the infants became icteric, two of them severely (both these infants died). No case of Rh incompatibility but one of A-B-O incompatibility occurred. This infant had only slight clinical symptoms of hemolytic disease and recovered.

Symptoms

The initial symptoms were generally vague and undiagnostic. In 13 infants the first symptom was either refusal of feeds or vomiting. Many infants were hypotonic and pale, a few excited and screaming. Six began with neurological signs such as rigidity, twitching, nystagmus or opisthotonus. Only three infants had fever and two or three tense fontanelle from the onset of symptoms. Two started with diarrhea, two others with cyanosis, and one with attacks of shallow breathing. The average age when the first signs were noted was 7.1 days with a range of 1 to 16 days.

The subsequent signs were mild in the three infants with serous meningitis but very severe in most of the 17 with purulent meningitis. Generally these infants rapidly became ashen gray, had cyanotic attacks, convulsions and often had rigidity with pronounced opisthotonus and tense fontanelle. Many had signs of shock, which could often be counteracted by means of cortisone and blood transfusions.

Temperature. No fever was found in the 3 cases of aseptic meningitis, in the cases of Listeria meningitis, and in 1 case of purulent meningitis in a premature infant (2150 g) where the diagnosis was only made at autopsy 5 days after birth. In 14 cases of purulent meningitis—8 caused by *E. coli* and 1 by Klebsiella—the maximal temperature varied between 38.1 and 40.1 C. In only five infants did the temperature surpass 39 C. Fever began between the second and the twentieth day of life. In eleven babies it did not start before they were 7 days old or more. Generally the fever lasted less than a week, but in 2 cases 10 and 16 days.

Cerebro-spinal fluid. The maximal cell count in the CSF was 57–1900 mononuclear cells per/mm³ in the infants with serous meningitis and between 700 and innumerable polynuclear cells per/mm³ in the purulent cases. In 2 of the latter bloody fluid was obtained, so that cell counts could not be made. In 1 of these culture revealed *E. coli*, in the other *Listeria monocytogenes*. This shows the importance of culturing even if the result of the spinal tap appears to be pure blood. In five instances cultures were negative but in three of these the infant had received some antibiotic treatment for one or more days before the first culture was performed. Total protein in the CSF ranged from 100 to 1500 mg %.

Case Reports

A few case histories are given to illustrate the variable symptomatology.

Case 1

Family history negative. The patient boy was the first of twins. The mother had anemia (65%) and urticaria 6 weeks before delivery. His twin sister weighed 3300 g at birth, was delivered by forceps, and died days old from tentorial tear. The patient

was born in breech presentation. Forceps were employed to deliver the head. Weight 2450 g, length 48 cm. He cried immediately. The day after birth he was a little rigid and had to be fed by gavage. On the third day diminished turgor of the skin but no neurological signs were noted. From the fifth day fever occurred, reaching a maximum of 39.5°C on the seventh day. He now cried when touched and began to vomit. On the eight day of life the fontanelle was a little tense. A lumbar puncture showed bloody fluid. No culture was performed from the first two blood mixed CSF samples; later no bacteria were grown from seven more samples of CSF. Nine thousand polymorphonuclear cells per mm³ and high protein values were found in the CSF. The patient was thought to have had an intracranial hemorrhage besides a purulent meningitis. Treatment consisted of penicillin (60 000 units twice a day for 3 weeks) dihydrostreptomycin (25 mg four times a day for 2 weeks) and a sulfa preparation (Alfasol) (200 mg six times daily for 1 week). The patient had rigidity and could not drink for 10 days, during which time the temperature was about 38°C. Head circumference remained normal. His subsequent development has been quit normal and he is doing well at school. Iatrogenic meningitis from one of the first two lumbar punctures cannot be complet ly ruled out in this case.

Case 4

Only child. Pregnancy normal. Boy born 4–6 weeks before term. Because of fetal distress forceps were used. Birth weight *000 g length 46 cm. Cried immediat ly. He became icteric on the third day without blood group incompatibility. On the seventh day his color suddenly became wax-like, his lips cyanotic and the respiration frequent and shallow. Lobeline and oxygen were administered as well as penicillin (30,000 units twice daily for 3 days). On the fifteenth day of lif he was intensely icteric, very irritable and f brile (39.5°C). From the sixteenth day several con ulsions occurred. Aureomycin (100 mg per day) was given for 4 weeks. A lumbar puncture was not performed before the infant was transferred to this department when .5 days old. Twenty-seven thousand polymorphonuclear cells per mm³ and *E. coli* bacilli were found. From the twenty-sixth day streptomycin was also given. The fontanelle gradually became tense. Head circumference was 40.2 cm shortly before he died at the age of months. The neuro-surgeon did not recommend surgical intervention. At autopsy severe hydrocephalus was found on the basis of meningoencephalitis and purulent ependymitis (no bacteria were cultured from later CSF specimens).

Comment. In this premature infant lumbar puncture should have been done on the *seventh day and sufficient antibiotic treat*ment should have been given early.

Case 10

Boy. Pregnancy and delivery were normal. The mother was unmarried. Birth weight 3200 g, length 50 cm. Nothing unusual was noted during the first days of life. At 5 days old h was transferred t an infants home preparatory t adoption. On the tenth day he vomited and the urine was dark. The next day the temperature was 40.1°C. he was hypotonic and had twitchings in the arms. Procaine penicillin (100 000 unit) was given i.m. and he was transferred t the pediatric department. A lumbar puncture showed ~3 ml yellow turbid fluid, with 10 000 polymorphonuclear cells per/mm³. Total protein 430 mg%. Culture revealed *Klebsiella*. The urine contained some erythrocytes and leucocytes but no albumin. Despite treatment with penicillin and streptomycin he died t 12 days. *At autopsy* fibrinous meningitis and hemorrhagic cyst itis were found.

Case 15

The mother who was 21 years old had had pulmonary tuberculosis. In 19.0 she had spontaneous abortion in the second month of pregnancy. During the last part of the present pregnancy (1959) he had slight album

...nuria and hypertension. Delivery which lasted 48 hours, was terminated by vacuum extractor The infant was not asphyxiated Birth weight 3800 g, length 5 cm. On the second day of lif he was a little jittery" and had slight rigidity of the extremities. Forty-eight hours after birth his temperature rose to 39.4°C. The fontanelle was tense and he had opisthotonus. H was transferred to the pediatric department. The CSF was purulent and organisms were seen and E col cultured. He became extremely ill with ashen gray color pronounced opisthotonus and "cerebral crying" His temperature remained slightly elevated for 16 days. On the fifteenth day he collapsed and looked as if he were dead, but he recovered after a blood transfusion in the tibial marrow without tests for compatibility Treatment consisted of penicillin (300 000 units twice daily for 3 days), duostreptomycin (a combination of streptomycin and dihydrostreptomycin) (45 mg three times daily for 13 days), sulphamethizole (200 mg three times daily for 22 days), etocortin (water-soluble hydrocortisone) (8 mg three times daily for 8 days), and acton prolongatum (ACTH) (5 units daily or every other day for 14 days) Besides this duostreptomycin (20 mg) was given three times intraspinally every other day from the second day of lif On the eighteenth day large hematomas suddenly appeared on both femora. They disappeared during treatment with vitamin K. During some periods phenobarbital was necessary We feared the development of hydrocephalus since as much as 15 ml of lear CSF could at times be obtained t lumbar punctures, but his head circumference was normal (40 cm) at discharge home when he was 2½ months old. His later physical and mental development has been normal, except that his teeth are somewhat brownish. When last seen t the age f 25 months he was bright and normal. No defect of intelligence hearing or vision was present.

Case 17

A girl, the result f the mother sixth pregnancy The first three pregnancies terminated in the f th and ght m the stillborn) th f l was extra t n pregnancy n l fifth is normal The al pregnanc w uneventful. The infan born in bre a present t m week est m t rm. Birth eight 30 length 13 cm N asphyxiated, became ic o on the ird d without blood gr up compa v Al rmal ser m bilir bi w 21 1 mg on the f urth da On the seventh day ser m bilirubin was 11 1 mg On the third day f f he somewhat m willing to drink d h r ankle jerks were increased bilaterall On f f rth day she suddenly became ven u h le being fed She was placed m an ncubat On the eight day she had t be fed b ga ge There was some tendency t y nou and pisthotonus. The eye mo ements w re floating Pure blood wa obtained by l mbar puncture Culture revealed *Listeria monocytogenes* Treatment duostreptomycin (40 mg three t mes daily) actocortin (10 mg three t mes daily) and itamin K_1 Despite this she died on the tenth day of lif Autopsy sh ed purulent meningitis, miliary granulomatous and horseshoe kidney The surface of the brain was co ered with widespread yellow-green pus and both lateral ventricles were filled with thin pus, containing numerous short, coarse gram posit ve rods. In the cortex and the whit substance of the brain diffuse smaller abscess es were found. Scattered through the liver small yellow granulomat and abscesses were seen. *Listeria* was cultured from dif ferent organs but not from heart blood t autopsy

Case 18

The mother had had pulmonary t berculosis. The infant, girl was the second hild The first a boy of 2½ years, is normal. During the last 4 days before deli ery the mother had severe aginal bleeding and received 4 l of blood. Her blood pressure dropped to 70 mm Hg syst lic. Cesarean section was performed 3 eeks before term because of placenta previa. Birth weight *650 g, length 49 cm. Respiration began after 2½ minutes and she cried 4 min tes after birth.

was born in breech presentation. Forceps were employed to deliver the head. Weight 450 g, length 48 cm. H cried immediately The day after birth he was a little rigid and had to be fed by gavage. On the third day diminished turgor of the skin but no neurological signs were noted. From the fifth day fever occurred, reaching a maximum of 39.5°C on the seventh day He now cried when touched and began to vomit On the eight day of life the fontanelle was a little tense. A lumbar puncture showed bloody fluid. No culture was performed from the first two blood-mixed CSF samples; later no bacteria were grown from seven more samples of CSF Nine thousand polymorphonuclear cells per mm and high protein values were found in the CSF The patient was thought to have had an intracranial hemorrhage besides a purulent meningitis. Treatment consisted of penicillin (60 000 units twice a day for 3 weeks) dihydrostreptomycin (.5 mg four times a day for 2 weeks) and a sulfa preparation (Alfasol) (200 mg six times daily for 1 week) The patient had rigidity and could not drink for 10 days during which time the temperature was about 38°C. Head circumference remained normal. His subsequent development has been quite normal and he is doing well at school. Iatrogenic meningitis from one of the first two lumbar punctures cannot be completely ruled out in this case

Case 4

Only child Pregnancy normal. Boy born 4–6 weeks before term. Because f fetal distress forceps were used Birth weight *000 g length 46 cm. Cried immediately H became icteric on the third day without blood group incompatibility On the seventh day his color suddenly became wax-like his lips cyanotic and the respiration frequent and shallow Lobeline and oxygen were administered as well as penicillin (30 000 units twice daily for 3 days) On the fifteenth day of life he was intensely icteric very irritable and febrile (39.5°C). From the sixteenth day several convulsions occurred Aureomycin (100 mg per day) was given for 4 weeks. A lumbar puncture was not performed before the infant was transferred to this department when .5 days old. Twenty-seven thousand polymorphonuclear cells per mm³ and *E. coli* bacilli were found. From the twenty-sixth day streptomycin was also given The fontanelle gradually became tense. Head circumference was 40.2 cm shortly before he died at the age of months. The neuro-surgeon did not recommend surgical intervention. At autopsy severe hydrocephalus was found on the basis of meningoencephalitis and purulent ependymitis (no bacteria were cultured from later CSF specimens)

Comment. In this premature infant lumbar puncture should have been done on the seventh day and sufficient antibiotic treatment should have been given early

Case 10

Boy Pregnancy and delivery were normal The mother was unmarried. Birth weight 3200 g length 50 cm. Nothing unusual was noted during the first day of life At 5 days old he was transferred to an infants home preparatory t adoption. On the tenth day he vomited and the urine was dark. The next day the temperature 40 1°C he was hypotonic and had t itchings in the arms. Procaine penicillin (100,000 unit) was given i.m. and he was transferred to the pediatric department A lumbar puncture showed ~3 ml yellow turbid fluid, 10 000 polymorphonuclear cells per/mm³ Total protein 420 mg%. Culture revealed *Klebsiella* The urine contained some erythrocytes and leucocytes but no albumin. Despite treatment with penicillin and streptomycin he died at 13 days. At autopsy fibrinous meningitis and hemorrhagic cyst were found.

Case 15

The mother who was 21 years old, had had pulmonary tuberculosis In 1950 she had a spontaneou abortion in the second month of pregnancy During the last part of the present pregnancy (1958) she had slight albu-

minuria and hypertension. Delivery which lasted 49 hours, was terminated by vacuum extractor The infant was not asphyxiated Birth weight 3600 g, length 52 cm. On the second day of life he was a little "jittery" and had slight rigidity of the extremities Forty-eight hours after birth his temperature rose to 39 4°C. The fontanelle was tense and he had opisthotonus. He was transferred to the pediatric department. The CSF was purulent and organisms were seen and E coli cultured. He became extremely ill with ashen gray color pronounced opisthotonus and "cerebral crying" His temperature remained slightly elevated for 16 days. On the fifteenth day he collapsed and looked as if he were dead, but he recovered after a blood transfusion in the tibial marrow without tests for compatibility Treatment consisted of penicillin (300,000 units twice daily for 3 days), duostreptomycin (a combination of streptomycin and dihydrostreptomycin) (45 mg three times daily for 13 days), sulphamethizole (200 mg three times daily for 23 days), actocortin (water-soluble hydrocortisone) (5 mg three times daily for 8 days), and acton prolongatum (ACTH) (5 units daily or every other day for 14 days) Besides this duostreptomycin (70 mg) was given three times intraspinally every other day from the second day of life On the eighteenth day large hematomas suddenly appeared on both femora. They disappeared during treatment with vitamin K. During some periods phenobarbital was necessary We feared the development of hydrocephalus since as much as 15 ml of clear CSF could at times be obtained at lumbar punctures, but his head circumference was normal (40 cm) at discharge home when he was 2½ months old. His later physical and mental development has been normal, except that his teeth are somewhat brownish. When last seen at the age of 25 months he was bright and normal. No defect of intelligence hearing or vision was present

Case 17

A girl, the result of the mother's sixth pregnancy The first three pregnancies terminated in the fifth, sixth and eight months (stillborn) the fourth was an extrauterine pregnancy and the fifth is normal. The actual pregnancy was uneventful. The infant was born in breech presentation 4 weeks before term. Birth weight 2230 g, length 48 cm. Not asphyxiated, became icteric on the third day without blood group incompatibility Maximal serum bilirubin was 1 1 mg % on the fourth day On the seventh day serum bilirubin was 11 1 mg %. On the third day of life she was somewhat unwilling to drink and her ankle jerks were increased bilaterally On the fourth day she suddenly became cyanotic while being fed. She was placed in an incubator On the eight day she had to be fed by gavage There was some tendency to cyanosis and opisthotonus. The eye movements were floating. Pure blood was obtained by lumbar puncture Culture revealed *Listeria monocytogenes*. Treatment. duostreptomycin (40 mg three times daily), actocortin (10 mg three times daily) and vitamin K_1 Despite this she died on the tenth day of life Autopsy showed purulent meningitis, miliary granulomatosis and horseshoe kidney The surface of the brain was covered with widespread yellow-green pus and both lateral ventricles were filled with thin pus, containing numerous short, coarse gram-positive rods. In the cortex and the white substance of the brain diffuse smaller abscesses were found. Scattered through the liver small yellow granulomata and abscesses were seen. *Listeria* was cultured from different organs but not from heart blood at autopsy

Case 18

The mother had had pulmonary tuberculosis. The infant a girl, was the second child. The first a boy of 2½ years is normal. During the last 4 days before delivery the mother had severe vaginal bleeding and received 4 l of blood. Her blood pressure dropped to 70 mm Hg systolic. Cesarean section was performed 2 weeks before term because of placenta previa. Birth weight 2650 g, length 49 cm. Respiration began after 2½ minutes and she cried 4 minutes after birth.

Oxygen was administered under pressure. The hemoglobin of the infant was 92% on the first day of life and 7 % on the second. On the third day she was somewhat flaccid with diminished skin turgor and was slightly icteric. No blood group incompatibility. On the fifth day she had *three short convulsions* and was transferred to the pediatric department. On the following days she was very apathetic, with a little shivering now and then. The bones of the scalp were overlapped and sunken. She had to be fed by gavage. On the ninth day opisthotonus supervened. A lumbar puncture revealed purulent fluid containing *Listeria monocytogenes*. Treatment with streptomycin, tetracycline, acetocortin and acton prolongatum was begun and continued for 3 to 4 weeks. The condition of the infant remained critical. She was apathetic, had opisthotonus, nystagmus, was dehydrated, but had no fever. She received four blood transfusions and intravenous fluids. No bacteria were grown from subsequent samples of CSF. Several times lumbar punctures and subdural punctures were "dry". Gradually hydrocephalus developed. At 1 month old she weighed only 2380 g. PEG and ophthalmoscopy were normal. At the age of months she was transferred to the neurosurgical department. Ventriculography showed massive internal hydrocephalus with formation of local intraventricular septa. The examination showed no stenosis of the aqueductus, but a relative block between the fourth ventricle and the cisterna magna. The ventricular fluid contained 4 mononuclear cell per/mm and 70 mg % protein. At the age of 3 months an anastomosis between the right side-ventricle and vena cava with insertion of a Spitz Holter valve was performed. This valve functioned well and the head circumference did not increase during the following months. It was 45 cm when the infant was discharged home at the age of 4 months. There was still some hypertonicity, increased tendon reflexes and strabismus. Her subsequent weight increase was satisfactory but her development is retarded. She could sit without support at 18 months and stand up and walk with support at 1 months. When last examined at age 22 months she could say several words. Head circumference was 48.6 cm. Strabismus convergens and increased tone in all extremities were present.

Comments

Complications

Two infants had pyuria as well as meningitis. One died of Klebsiella meningitis. Cystitis but no urinary tract malformations were found at autopsy. The other has not had further urinary tract infections and is completely normal. In 1 case (Case 17) horseshoe kidney was found at autopsy but this has probably nothing to do with the fatal outcome of her Listeria infection. No cases of spina bifida or congenital urinary obstructions were found among our cases. Subarachnoidal hemorrhage was probably present in 1 case (Case 1) before a diagnosis of purulent meningitis was made.

Hydrocephalus developed in 6 cases. Four of these died (—, ½, 4 and 9½ months old). Three of these were due to *E. coli*; in the fourth no growth was found after 5 days treatment with penicillin. Only one of these infants had been operated upon (ventriculo-peritoneostomia at 5 months). The two surviving children both had operations for their hydrocephalus. One girl (Case) with purulent meningitis of unknown etiology had rachipleurostomy at the age of 3 months. She is a little retarded. She began to walk without support at 17 months. At the age of 5 years she knows several letters. She has no neurological signs but her head is large (circumference 60.5 cm). The other surviving patient (Case 18) has cerebral palsy.

Treatment

The treatment of meningitis of the newborn is difficult. Before the result of culture and the determination of susceptibility to antibiotics is known combined treatment consisting of intramuscular injections of streptomycin (50 mg per kg per 24 hours), sulpha preparation (400 mg per kg per day),

and tetracycline (60–100 mg per kg per day) is recommended. If *E. coli* or Listeria is cultured from the CSF this treatment should be continued for 3 weeks or longer as indicated by the clinical response and the CSF findings. The two latter compounds can be given orally when feasible. In case of shock—which is likely to occur in *E. coli* meningitis—noradrenaline or cortisone and corticotropin plus blood transfusions should be given. Intrathecal treatment which is not recommended by Margaret Smith (18) unless *Pseudomonas aeruginosa* is found, should, in my opinion, be given in *E. coli* and Listeria meningitis in the form of duostreptomycin (20 mg intra-spinally to a full term infant). This form of treatment will be further discussed below. When incipient hydrocephalus cannot be prevented by repeated lumbar punctures ventriculo-cavo-anastomosis with Spitz Holter valve should be performed. Subdural effusions should be looked for and treated as indicated.

Prognosis

No fatal cases occurred among the three children with *serous meningitis*. One of these had a birth weight of only 1000 g. She is now 10 years old and slightly retarded with an IQ of 62 %. Another child had congenital anal atresia and has slight behavior difficulties (his father committed suicide years ago). These abnormalities are probably not to be classed as sequelae of their meningitis. The third child is completely normal.

The mortality in the different groups of *purulent neonatal meningitis* has already been shown in the table. Eight of the 17 babies died (47). Among the 9 cases of *E. coli* and coliform infections 5 died (56 %). It is possible that the series in reality contains 11 cases of coliform meningitis, 7 of whom died (63). All the 9 cases of *E. coli* or Klebsiella meningitis occurred in boys. The mortality was 50 % in boys (7 of 14) and 33 % in girls (1 of 3).

Hydrocephalus developed in 35 % of the cases of purulent meningitis. Their fate has been described above. In 2 more cases transient signs of hydrocephalus occurred. Both have developed quite normally. They were treated with repeated lumbar punctures.

Follow up. Only two (.5 %) of the infants who had *E. coli* meningitis have made a complete recovery. Among the total of 1 survivors six were found to be completely well and normal. Three are slightly retarded. One has impaired hearing. Two have minor behavior problems. Only one child (Case 18) is seriously handicapped.

Age at last follow up. Twelve survivors, average age 5.4 years, range 1.3–10.5 years. All the children except one were examined by the author. No connection between the time of onset of the first symptoms and the final outcome was found, but early treatment was important both regarding mortality and morbidity.

It is seen that the prognosis—especially considering the etiology—has improved in the last five year period during which treatment has been started earlier and has been more comprehensive. In the present series the prognosis was only slightly worse in premature as compared with full-term infants.

Intrathecal treatment. Three cases of *E. coli* meningitis had intrathecal treatment (two or three intralumbar injections of 20 mg duostreptomycin). One of these infants died (mortality 33). Among 5 cases of *E. coli* meningitis who had no intrathecal treatment 3 died (mortality 60 %).

Period	No. of cases	Average age at start of treatment	Inadequat treatment
1950–54	10	13.3 days	6
1955–59	10	8 6 days	1

Period	No. of cases	Coliform	Listeria	Serous	Died	Living	Normal
1950–54	10	3 (3?)	0	3	5	5	3
1955–59	10	6	2	0	3	7	3 (4?)

Discussion

If only the 17 cases of purulent meningitis of the newborn are considered the mortality was 47 %. This is about the same as found by Dupont & Thamdrup [2] who had five deaths among 9 cases and as in the series of Mogensen *et al* [1_], where 14 of 25 died Among our 9 surviving purulent cases only 4 were completely normal at the time of the follow up Again this corresponds with the other two series, where about 40 % of the surviving children were found to be completely cured It is evident that the prognosis, especially in cases of *E coli* and Listeria meningitis, is still very bad. As exemplified in Case 16 complete recovery is possible even if the infants are extremely ill. Early lumbar puncture is recommended even if symptoms are vague as is vigorous treatment as described above

Subdural effusions were not demonstrated in any of our infants. According to the literature such effusions (frequently bilateral) are often found in the course of purulent meningitis in young infants [14 19]. Platou *et al* [14] found such effusions in 53 patients among 343 cases of purulent meningitis in children less than 3 years old. They do not state how many of their cases were due to neonatal *E coli* meningitis Even when these fluid collections were treated with subdural taps until dry" the incidence of severe neurological and mental sequelae was much higher than in cases where such effusions were not found or suspected. The indications for subdural taps in infants with meningitis have been described by McKay *et al* [11] Subdural puncture was only performed in five infants in the present series, but if the effect of treatment is not completely satisfactory this examination should certainly be done

Prophylaxis As described in more detail by Debré *et al* [1], large doses of penicillin should be given to both mothers and infants in case of fever premature rupture of the membranes, premature deliveries, multiple pregnancies complicated or difficult deliveries. It has not yet been stated which form of treatment is most likely to prevent penicillin-resistant infections in the infant without risk of unpleasant side-effects

Summary

Twenty cases of neonatal meningitis from the period 1950 to 1959 from the Rigshospital Copenhagen have been analyzed and followed up. Sixteen of the infants—including all the 8 cases of *E coli* meningitis—were boys. Three-quarters occurred during autumn and winter One-third of the infants were premature \

similar number were asphyxiated at birth. Delivery was complicated or difficult in three quarters of the cases.

There were 3 cases of serous meningitis with no deaths. One of these children is slightly retarded (birth weight 1000 g). Among the 17 cases of purulent meningitis, CSF cultures were sterile in 5 cases. One of these infants died, another had an operation for hydrocephalus and is probably a little retarded. Eight cases were due to *E. coli*. Four of these died, 3 with hydrocephalus. Among the surviving cases of *E. coli* meningitis one has somewhat impaired hearing and another has a little behavior difficulty. One baby with Klebsiella meningitis died in the neonatal period. Of 2 cases of Listeriosis one died and the other has cerebral palsy and some mental retardation (operated on for hydrocephalus). Six infants developed hydrocephalus and four of these died.

The initial symptoms were vague. Refusal of feed was the first symptom in most cases.

Early and intensive treatment was found to be important. The mortality in *E. coli* meningitis was less in infants given streptomycin intrathecally than when such treatment was not given. Although our material is too small to draw any definite conclusions from this, such treatment should be given in purulent meningitis neonatorum until proved ineffective or noxious. I feel that supportive treatment with steroids and blood transfusions is very important. The best form of prophylaxis has not yet been established.

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Pediatric Department
Rigshospitalet
Copenhagen
Denmark

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From the Institut for the Care of Mother and Child (Pediatric Head. K. Poláček), Prague, Czechoslovakia

Renal Function in the Respiratory Distress Syndrome

by RUTH L. CORT

The so-called respiratory distress syndrome, occurring chiefly in premature infants and associated with a high mortality has been the subject of intensive study in recent years. The syndrome is associated with a number of cardiovascular respiratory and metabolic disturbances, which have been reviewed by James [9]

This report concerns the excretion of nitrogen, water and electrolytes in the urine of 13 premature infants with the respiratory distress syndrome 7 of whom survived, and 6 of whom died within 1–2 days after birth.

Methods

Urine collection was begun as early as possible after birth, as soon as suspicion of progressive respiratory distress arose (usually within 2–4 hours after birth). The method used permits frequent collection of small amount of urine [5].

Urine was analyzed for tot l N (micro-Kjeldahl) urea (see below) Na and K (Zeiss flame photometer) and Cl [3]. In 12 cases urinary inorganic P was also determined [8]. Urine collection was continued for 4½ days in surviving infants. Any milk gi en was analyzed for N Na, K and Cl.

Heel blood samples for hematocrit and urea determinations were taken 1 hours after birth, and at daily interval thereafter. Capillary tubes were used for hematocrit determinations, and readings were reproducible within %. Blood urea was determined by the ultramicro method f Caraway & Fanger [1].

Four normal premature infants, studied for another purpose served as controls. They were given only 5% glucose feeds for two days after birth. They were somewhat larger and more mature than the ill infants (2–4 weeks longer gestation)

"Urea production" was calculated from the rise or fall in urea content of body water (assuming body water to form 80% of body weight), and the amount of urea excreted in the urine. Since umbilical cord blood urea levels were not vailable they were assumed in all cases to be 15 mg% [16].

All infants were nursed in incubator (Isolett), with maximal humidity and ambient temperatures of 31–32 C. All were sedated with chlorpromazine or allobarbital in moderat to low dosage [20], and received prophylactic antibiotics.

An ttempt was made to correlat changes in linical signs f respiratory distress with the course and nature of urinary excretion. Two broad groups f clinical respiratory bnormality were distinguished, called for convenience the dyspneic and "depressed" types. In the first labored respiration with varying degrees of cyanosis predominated and in the second, extremely superficial bdominal respiration with good oxygenation, a judged by color was in striking contrast to the first group. It must be emphasized, however that these divisions were arbitrary

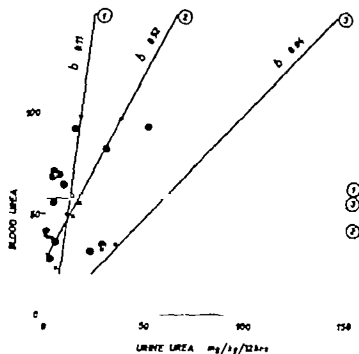


Fig 1 Relationship between blood urea and urine urea (mg/kg/12 hours) in (1) dying (○), (2) depressed (×) and (3) dyspneic (●) infants during the first 36 hours of life. b-regression coefficient. Average blood urea values for each group are shown.

TABLE 1 *Birth weight average body temperature blood urea and peripheral hematocrit at 12 hours in normal premature infants and 13 infants with respiratory distress (see text) Body temperatures are averages of 3-hourly rectal temperatures 0–36 hours after birth*

Group	No.	Birth weight	Av body temp.	Blood urea 12 hrs	Blood urea 24 hrs	Hematocrit
Normal	4	2200 ± 45	36.4 ± 0.2	34 ± 13	47 ± 19	59 ±
Dyspneic	5	1630 ± 190	35.3 ± 0.5	51 ± 13	73 ± ..	53 ± 3 (3 infants)
Depressed	2	1525 ± 5	34.3 ± 0.1	39 ± 7	60 ± 2	76 ±
Dying	5	1670 ± 700	35.1 ± 0.6	53 ± 9	80 ± 10	73 ±
Dying	1	1000	35.9	53	4	59

It was often difficult t predict within the first 12 hours into which group a given infant would fall, and subsequently signs often alternated within a few hours. For example infant 1 showed features of the "depressed type of respiratory disturbance on the third day of life, although she had typical retraction and cyanosis the first day of life (see Fig 2)

Dying infants all had severe respiratory distress of the dyspneic type, with the exception of the last infant (presented separately), in whom from birth cyanosis was profound in the face of definit but only moderat dyspnea. On post mortem, the cause f death in this infant was found t be a tentorial tear with extensive intracranial hemorrhage. In the remainder respiratory failure was judged to be the primary cause of death.

Results

Table 1 shows the birth weights, average rectal temperatures, blood urea levels and peripheral hematocrit level for five groups of infants, during the period 0–36 hours after birth. The "depressed infants (numbers 3 and 4 Fig. 2) were smaller than either the dyspneic or dying groups, and had lower body temperatures and blood urea levels. The peripheral hematocrits of these two infants were high, as were those of infants who clinically and on post mortem examination, were judged to have died of respiratory failure.

It was repeatedly confirmed that these very high hematocrits were not related to difficulty or ease in obtaining blood samples from skin punctures. Indeed, the readiness with which premature infants particularly ill ones, bleed from heel punctures is often in marked contrast to the typical cutaneous "bloodlessness" seen in mature newborn infants

The peripheral hematocrit has proved a reliable prognostic finding diagnostic of fatal respiratory distress in cyanotic infants at 12 hours of age Four infant with

Fig. — Urinary excretion of water electrolytes and urea in 4 infants with respiratory distress. Infant 1 and 2 are dyspneic and infant 3 and 4 depressed Curves from above: 1, blood urea (mg%); 2, urinary N K (mEq/L); 3, urinary K (mEq/L) (the difference between and 3 is therefore urinary Na concentration); 4, urinary urea concentration (mg); 5, urinary olume (ml/kg 3 hours).

A, B, C and D indicat approximat severity of clinical signs. A, cyanosis, including major pause at echo; B, dyspnea, retraction and rapid labored respiration; C, respiratory depression, superficial abdominal respiration without regard to regularity or rate; D edema.

Lower half of graphs: 12-hour balances of Na, K and Cl and urinary P (*see key on right*). 1 hour urea production (mg/kg); 12 hour urine olume (ml/kg).

Infusions of glucose (Gl) or plasma (Pl) are indica ed.

TABLE 2. *Urine volume and total urinary output of Na K and Cl in the same groups of infants as in Table 1 All data are expressed per kg per 36 hours*

Group	No.	Urine volume	Total urinary output mEq K	Na	Cl
Normal	4	19±1	0.64±0.17	0.61±0.40	0. 0±0.52
Dyspneic	5	26±17	1.01±0.36	1.05±0.59	1.04±0.64
Depressed	2	4±1	0.20±0.06	0.21±0.06	0.06±0.02
Dying	5	7±3	0.27±0.16	0.66±0.28	0.6 ±0.22
Dying	1	*7	0.75	1.23	1.62

cyanosis and moderate respiratory distress who died had hematocrits within the normal range at 12 hours, but on post mortem, the causes of death were found to be transposition of the great vessels, hemorrhage Waterhouse-Friderichsen syndrome and mechanical brain trauma The last infant is shown separately in the tables, and is the last infant in Fig. 4

Table * summarizes the urinary output of electrolytes in the same five groups of infants. In those dying infants (3) who did not survive a full 36 hours, the data obtained during life (in all over *4 hours) extrapolated to 36 hours to permit ...son with the others. The fluid intake of all groups was similar and small

The marked oliguria of depressed" and dying infants is striking and appears to be a constant feature of fatal respiratory distress from another five cases observed, but not reported here As in the case of the peripheral hematocrit the presence of normal values of urinary output point to some other cause of death in a distressed infant than pure" respiratory failure

Both depressed and dying infants excreted less urine containing less electrolyte than dyspneic infants who survived Those infants who died however showed the retention of K in the face of relatively high Na output reported in full term infants after difficult birth by McCance & Widdowson [11], and commented upon by other authors [4 0] They also passed amounts of Cl about equal to Na while depressed infants strikingly retained Cl If these three electrolytes measured in fact reflect acid base adjustments occurring in the urine such a situation means a significant quantitative handicap in excretion of anion (presumably primarily organic acids) to the infants who died.

The figures for "unidentified anion excreted by the various groups of infant are shown below:

Group	Na + K − Cl, mEq/kg/36 hours
Normal	0.53
Dyspneic	0.98
Depressed	0.35
Dying	0.31
Dying (1)	0.48

None of the infants who died had any detectable amount of inorganic P in the urine but since all of the other infants studied had very small amount of urinary P in the first 1-_ days of life the quantitative significance of phosphate-buffering deficiency in the infants who died is not clear

Table 3 shows the calculated "urea production and the data employed to

TABLE 3 *"Urea production" per kg and approximate urea clearance per kg per 12 hours in the same infants as in Table 1 (Omitting the last "dying" infant)*

Group	No.	"Urea production	Average blood urea	Urine urea kg/12 hrs	Regression coefficient
Normal	4	340 ± 233	41	33	0.69
Dyspnoeic	8	493 ± 153	58	89	0.94
Depressed		25_ ± 11	4_	8	0.52
Dying	5	821 ± 67	60	13	0.11

calculate the approximate urea clearance in the same infants. Although the variation found was considerable the depressed infants did appear to have urea productions markedly lower than dyspnoeic infants, and probably lower than normal infants. In fact, the blood urea levels of the depressed infants rose to the same extent as those of normal infants the first 36 hours of life in the face of a very much lower urinary output.

The final column of Table 3 gives the regression coefficients of urinary urea/kg/1_ hours upon blood urea levels. The data in all infants with respiratory distress are illustrated in Fig 1 It is clear that in general infants who died had profoundly depressed urea clearances. In two of the

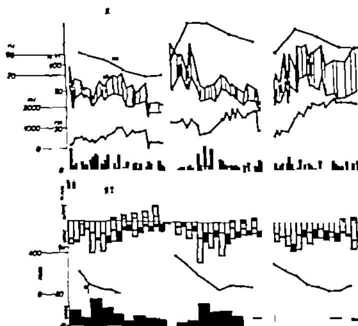


Fig. 3 As Fig _, three dyspnoeic infants (see Fig 2 for explanation of curves).

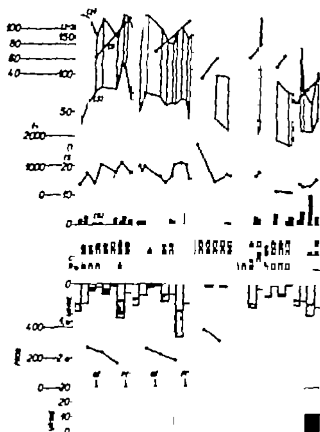


Fig 4 A Fig. 2 and 3, six dying infant (see Fig for explanation of curves). The last infant is presented separat ly in T bles 1 and (see text).

infants (first two Fig 4) the "clearance" fell within normal limits the first day of life and then deteriorated until death These infant survived the longest—over two days

The infant who survived were followed for four and a half days after birth, and the balance data obtained in all infant with respiratory distress are presented in detail in Figs. 2 3 and 4

The first feature of interest to be noted is that a more or less abrupt diuresi oc curred in dyspneic surviving infants with simultaneou and marked increases in 'urea clearance Thi i best seen in in fants 5 and 6. Although the rise in urine volume was gradual in infant 1 and less dramatic in infant " particularly in the latter an increase in urea clearance occurred in the fourth period (the second half of the second day)

This diuresi was constantly associated with improvement in clinical condition, especially color Abrupt rises in urinary volume usually occur at some time during the first ?–?½ days of life and are seen also in normal premature inf nt almost without exception (8).

Secondly by and large dy pnea was associated with a relat vely h gh urinary Na concentration and respiratory depression with relative Na retention The exceptions

appear to be infants 3 and 4 the "depressed" infants. These two infants, however showed considerable instability of clinical signs, and observation was not sufficiently frequent to be certain just how long the periods of respiratory dyspnea, occasion ally seen in both lasted. It is tempting to associate the two peaks in urinary Na concentration in infant 4 with the two discrete periods of apnea and cyanosis, but the same clear association in time was not seen in infant 3.

A drop in urinary electrolyte concentration, particularly Na concentration, coincident with the disappearance of dyspnea was clear in infant 1 (where slight dyspnea continued right up to the onset of diuresis, although incorrectly shown in Fig. 1) and to a lesser extent in infant 6 That the onset of diuresis, though important prognostically did not always herald a trouble-free convalescence is evident from the courses of infants 2 and 5. Both improved t the time of diuresis, but both continued to have respiratory difficulties for several days more so in infant 2.

The ffect of infusions

Since a systematic study of the effect of infusions of various types upon the course of the respiratory distress syndrome is only now under way only a few observations can be made here

On four occasions single infusions of 10 % glucose (8–10 ml/kg) with B vitamins were given to infants 1 3 and 5. They were in all cases followed by either maintenance or increase in the urinary concentrations of urea and electrolytes, with no marked change in the character of the urinary constituents measured.

The effect of 8 ml/kg of plasma with 10 % glucose was very dramatic in the case of infant 2 at the end of the third day A large diuresis followed, without urinary dilution, except that the urinary Na concentration fell temporarily There was an increase in urinary urea concentration and "urea clearance" with prompt fall in blood urea. Any detectable effect of an infusion of 5 ml/kg plasma upon urinary excretion was delayed for almost 12 hours in infant 4 when an increase in urine volume of modest proportions occurred, with increase in urinary urea concentration. Whether the change in predominant clinical signs from dyspnea to depression can be related to the infusions will require further study

Infusion did seem to lead to increases in body temperature, however which were small with glucose but larger and prompt in the case of plasma infusions. Thus, comparing the body temperatures of the four infants who received glucose in the 1. hour periods preceding and following infusion, they rose on the average $0.41 \pm .10$ C, and in the two infants who received plasma, $0.80 \pm .08$ C.

Discussion

These observations were not designed to be and are not, an exhaustive study of the renal adjustments of premature infants to the multitude of metabolic disturbances accompanying the respiratory distress syndrome They had their origin in clinical observations of the course of the disease and the impression that babies who fail to survive this syndrome are virtually anuric from a very early stage

These studies are not concerned with the primary cause of respiratory failure

but rather with the mechanisms of survival available to premature infants suffering from it

When one compares infants who survive the respiratory distress syndrome with those who do not depression of renal function (i e. urine volume passed and "urea clearance") is found in the latter There are also qualitative differences in that dying infants tend to excrete *relatively* more Na and less K than surviving in fants Dying infants also have extraordi narily high peripheral hematocrits by 12 hours after birth.

The combination of low urinary outputs and high hematocrits at 12 hours seemed to be a reliable indication of fatal termina tion with "pure respiratory failure in dyspneic new born premature infants. The two depressed" infants also passed very little urine and had high peripheral hema tocrits, and they survived Their renal function was not as low as in the dying group however and it also seems fair to conclude from their low body tempera tures the slow rise in blood urea and their clinically good oxygenation, that they did not in fact need to rid themselves of large amounts of metabolic end products as did dyspneic infants.

In view of the series of metabolic and cardiovascular abnormalities consequent upon respiratory failure respiratory and metabolic acidosis [9] high serum K with ECG changes [18] hypotension [1?] other signs of cardiac failure [9], etc one is not surprised to find abnormalities in renal function as well a has been pointed out by James [9].

Observations in almost ?0 infant with respiratory distress suggest however that failure of *renal function reflect a process* intrinsic to the pathogenesis of fatal respiratory failure rather than being merely a complication or terminal phenomenon. There are both quantitative and qualitative abnormalities in the infants who died of the respiratory distress *syndrome* The most likely explanation for the quantitative differences presented here is that renal blood flow is low in infants destined to die This may be due in part to systemic hypotension [12]. The presence of high hematocrits suggests an additional factor —low blood volume. The report of Sutherland *et al* [17] on the accumulation of edema in the legs of infants with respiratory distress would lend support to this hypothesis, since the source of peripheral edema is presumably the vascular compartment. The work of *Clark & Gairdner* [-] also suggests that a large shift of plasma out of the blood soon after birth may be a common phenomenon in new born infants.

The logical step of relating the time course of changes in packed cell volume presumably reflecting plasma shift to the time course of urinary volume in premature infants seems justified. In fact the peripheral hematocrit has been found to be consistently related to urine volume a high hematocrit with a low volume and conversely both in ill and well infant [6]

According to Pincu *et al* [14], peripheral hematocrits up to 0 are not uncommon in premature infant the first day of life The relation between the central venous and peripheral hematocrits requires study however The differences may be large in normal new born infant but values in two infant with respiratory distress were found to be only -- [6]

The suggestions made that infant wh

die have low blood volumes, and never achieve a degree of oxygenation sufficient to mobilize interstitial fluid to correct this volume deficit. A further series of processes similar to those seen in refractory adult oligemic shock [13] may contribute to failure to mobilize both interstitial fluid and stagnant blood into the effective circulating blood volume. These include extreme arteriolar vasoconstriction and venous pooling of blood. The readiness with which our ill infants bled (very dark blood) from skin punctures might have resulted from tapping pooled venous blood.

The qualitative differences between dying and surviving infants involved chiefly the proportion of Na and K excreted in the urine. Infants with dyspnea had high concentrations of N in the urine and those who died in addition retained K. This pattern of excretion may be due to partial adrenal insufficiency in view of the report of Cranny & Cranny [7] that ill premature infants excreted less 17-hydroxycorticosteroids than well ones. Salmi and co-workers [15] showed, however, that newborn premature infants were capable of high outputs of 17 hydroxycorticosteroids. It is possible that the severe stresses of anoxia and acidosis lead to early exhaustion of adrenal function in this condition. An additional factor may contribute to adrenal malfunction—if the kidneys are poorly perfused with blood, may not the adrenals also suffer from vascular insufficiency?

The implications of the findings reported here for therapy of the respiratory distress syndrome would be clear if this syndrome involved only circulatory collapse and renal failure of the type seen in adult oligemic shock or infantile fluid depletion. Not only is it as yet unclear which of the many abnormalities in this syndrome is primary and/or most susceptible to treatment, but the time course of disturbances is telescoped and its onset can usually be related to the circumstances of birth [10].

Therapy thus far in our department has involved chiefly what might be termed supportive measures—attempts to minimize the adverse effects of hypoxia through sedation [20] and to treat some of the more urgent metabolic problems such as K accumulation [19].

A cautious trial of the effects of expanding plasma volume (or rather of preventing its decrease) would seem warranted. This could be expected to support a high rate of blood flow in the pulmonary circuit, to maintain renal function in order to correct with maximum efficiency and speed acid base disturbances and to relieve the distortion of cardiovascular function secondary to high blood viscosity and low blood volume.

Summary

The urinary excretion of N, urea, water, Na, K, Cl and P were studied in 13 premature infants with the respiratory distress syndrome, 6 of whom died. Studies were continued for a maximum of 4½ days after birth. Urinary findings were correlated with clinical signs of respiratory abnormality. The following conclusions were drawn.

1. Infants who die with pure respiratory failure have generally depressed renal function, evident in low urinary volume and urea clearance. In view of their high peripheral hematocrit 1 hours after birth, low renal function was ascribed to low renal blood flow due to

low blood volumes, among other cardiovascular abnormalities

° Dying infants also excrete relatively more Na and less K in the urine than dyspneic infants who survive Their excretion of unidentified anion (presumably primarily organic acids) is probably handicapped by both the quantitatively low urine output and relatively high rates of Cl excretion

3 Two infants with predominantly depressed respiration appeared to have low metabolic rates, with lowered body temperature a slow rise of blood urea low urinary outputs and high hematocrits

4 In general dyspnea is associated with high and respiratory depression with lower urinary Na concentrations

5 The frequent occurrence of a more or less abrupt diuresis in ill and well premature infants at some time during the first 2–2½ days of life has been observed. This diuresis in dyspneic infants i associated in time with clinical improvement particularly in color

6 The suggestion i made that maintenance of plasma volume is indicated in treatment of the respiratory distress syndrome

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Institut for the Care of Mother and Child
Praha 4, Podolí
Czechoslovakia

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CASE REPORT

A Case of Non lipoid Granulomatosis (Letterer Siwe Disease) Observed for 15 Years

by DAN HOLMLUND

From the Medical Department (Head H Kroel, M D) Vänersborg Central Hospital

In 1940 Wallgren [7] suggested that Letterer–Siwe disease and Hand–Schüller–Christian disease were in reality the same malady and that their different features were explicable when the age of the patient and the duration of the malady were taken into account. In 1941 Farber suggested that eosinophilic granuloma was also a variant of the same disease process

Nowadays most clinicians and pathologists agree that Letterer–Siwe disease Hand–Schüller–Christian syndrome and eosinophilic granuloma are variants of the same malady—nonlipoid reticulo-endotheliosis Not until the etiology of the reticulo-endotheliosis is understood will it be possible to prove this hypothesis.

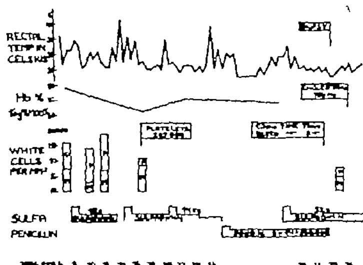
Case History

Boy born on July 1 1944 Birth weight 4100 g The patient is number four of eight siblings. The parents and their other children are healthy The boy s early development was normal. H was in good health till December 1945 when he contracted eczema of the scalp. At the same time lymph nodes appeared in his neck, and he had periods of high fever On February 6, 1946 he was admitted to the Pediatric Department of the Halmstad Central Hospital. On admission, lymph nodes up to the size of a plum, were observed in his neck. H had no rise of temperature and the rashes were of moderate severity Soon however widely spread petechial rashes appeared, and he had periods of high fever The lymph nodes in his neck increased in size Both the spleen and the liver were palpable about 3 cm below the arcus costarum. X ray examination of the lungs showed an infiltrat big as a child palm, in the cardio-hepatic angle This infiltrate remained for some months. Radiological surveys of his skeleton showed no abnormality at this time

Laboratory findings, treatment and course during the first three weeks in hospital are best illustrated by Table 1

Biopsy of a lymph node the neck showed (Professor Ahlström) A huge proliferation of elements, resembling reticulum cells, is seen within the extirpated lymph node These elements form broad zones or large accumulations, localized rather uniformly within the parenchyma of the node The parenchyma is forced out of its place but here and there however one can see isles of normal lymphoid tissue with reaction centers which detach themselves distinctly from the accumulations of proliferating reticulum cells. The presence of eosinophilic leukocytes within these accumulations is striking Sometimes the eosinophilic leukocytes lie diffusely arranged, but fairly often they gather to small, almost abscess like centers The capsule of the lymph node is preserved No Sternberg cells can be found There are no signs of tuberculosis. It is difficult to make a definite diagnosis. The possibility of a lymphogranulomatosis may be considered but the partially preserved structure of the lymph node as well as the absence of tem

TABLE 1 *Chart of the temperature blood counts and therapy during th first weeks of illne s*



berg cells does not indicat it. The picture does not correspond t leukæmia of myelogenous or lymphogenous type One must, however carefully consider *reticulo-endotheliosis of Letterer–S ise type*, and the clinical features seem to correspond very well t it The presence of eosinophilic leukocytes is striking, but may occur in variants of this disease

Bone marrow biopsy showed (Doctor Elsa Segerdahl): "The marrow is rich in cells and of normal ppearance considering leukopoenia well as erythropoiesis. The latter is rather active with few centra of normoblasts. The megakaryocytes are normal. There is no increase of reticulo-endothelial lements. N pathological forms can be observed.

The course of the disease slowed down after some months. The petechiae disappeared, the temperature was normalized, the lymph nodes became smaller and soon the spleen could not be palpated. The liver however wa still palpable about 3 cm below the arcus costarum. On May 9 1946, the boy was ble t lea the hospital in a fairly good cond tion

On Jul 20 1946, however he was re-admitted because of troublesome suppuration from the right ear On admission to hospital suppurating antrum-otitis with large granulations was observed. A modified radical operation was carried out

The microscopic examination of the material showed (Professor Ahlström): "The tissue from the processus mastoideus shows small spongiously spread osseous lamellae enclosing bone marrow of normal ppearance However one can also see a very cellular granulation tissue consisting of often rather closely stored histiocytic cells and f eosinophilic leukocytes, which, in places, form compact carpet and entirel dominate the picture Here and there necroses can be found. There are few multinuclear giant cells. The process infiltrates within the mucous membrane f the cellular system, and the osseous lamellae show lacunary resorption. By fat staining numerous fat-carrying cells ppear which are accumulated especially within the mucosa and within fibrously transformed part of the marrow between the small spongious osseous lamellae The observed changes are of the same type as those that have earlier been described in the l mph node Consequently an eosinophilic granu

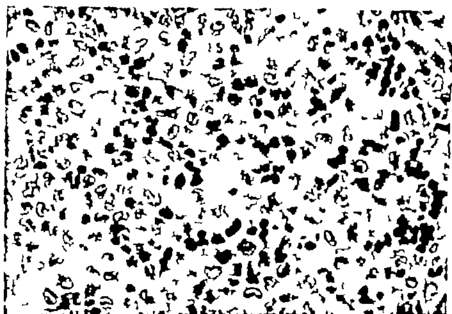


Fig. 1 Microphotograph of section of a cervical gland. Biopsy t 18 months. 400.

lomatosis of the same type as can be observed within the group Letterer–Siwe d sease–eosinophilic granuloma–Schüller–Christian disease The percentage of f t indicates an incipient maturity of the process."

In spit of the mastoid peration, the ear was still suppurating Another operation was carried out Sulfa drugs and penicillin were administered. They had no effect On November 15 1940, after four month of vain attempts, the right ear was gi en radiological treatment This seemed t have in fluenced the process favourabl and, about a month later the ear was dry

In the meantime however the process continued in other places. In December 1946 a swelling appeared on the right over-arm. This swelling was due to process in the



Fig — X ra of the right humerus a, 17.XII 1946 b I X 1961

humerus. Roentgen examination showed an area of translucency as big as a Brazil nut, with a considerable thickening of the bone The corticalis was quite broken through (see Fig. *)

At the same time the boy had severe gingivitis. The mucosa became partly ulcerated. The teeth became loose. A desquamating seborrheic eczema could be seen on the scalp. From January to March 1947 the patient had several periods of fever and petechiae appeared now and then. In addition, soft lesions, which could also be followed roentgenologically were palpated on the skull. X-ray examination showed new lesions in the arms, legs and ribs.

Laboratory findings. Hemoglobin 53% –74% (8.5 g%–11.8g%) Sedimentation rate 40–60 mm. Leucocytes 6000–11 000 per mm³ (segmented neutrophils 71%, eosinophils 3%, lymphocytes 25%, monocytes 1%). Platelets 250 000 per mm³ Body weight 12.5 kg

The patient was treated essentially with penicillin, sulfa drugs and roentgen therapy locally to the lesions (see Table 2).

From March to July 1947 there were no essential changes of the course. Certainly the osseous lesions increased, but the general condition was unaltered. On July 5, 1947 the boy was discharged. His mother was urged to come back with him for follow-up one month later but she did not do so.

According to his mother the boy was very feeble after his stay in hospital. He stumbled over thresholds, ate poorly etc. When he was 3 years and 6 months old, his mother noticed for the first time that he could not hear Evidently his deafness came on rather suddenly. No doctor was consulted.

At the age of four the boy began to drink more and more In the day he usually drank up to 1 litre an hour and in the night he drank about 7 litres. A severe diuresis followed. For 3 years, his mother had to change his bed-clothes 2–3 times every night In June 1952, when she could not manage any longer she brought the boy to the Halmstad Central Hospital.

On admission, the boy was small and very thin for his age His weight was 16 kg His head was big, of hydrocephalus type and somewhat flattened at the back of the neck. The circumference of the skull was 57 cm. He leaned his head to the right No defects of the skull could be palpated. A considerable exophthalmus and a slight divergent strabismus was noticed. The boy was deaf.

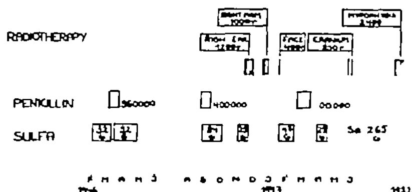
X-ray examination of the skull revealed scattered, sharply demarcated, rounded areas, characteristic of Hand–Schuller–Christian disease (see fig 3).

Laboratory findings The average amount of urine in 24 hours was up to 7 litres, but all the urine could not be collected Specific gravity 1.006. Chlorides in urine 0–3 mEq/litre



Fig. 3. X-ray of the skull. a, 9 IV 1947 b, 9.XII. 1960.

TABLE 2 *Chart of th treatm nt*



The patient received roentgen therapy to the hypophysis. The result was excellent (see Table)

In 1953 the boy's schooling was discussed. A special school for mentally retarded, deaf children seemed to be the best for him. During the first few years, it wa very dif ficult for him to keep pace with his school fellows in games and acquirements. Soon however he leveloped so well both physi cally and psycl ically that his teachers thougl t that he ought to attend an ordi nary deaf and dumb school. This change however did not turn out well because he could not adapt hims lf to the new environ ment The result wa an noct unal enuresis.

F r a thorough ex minat n of this en resis, particularly with a new t a possible



Fig 4



Fig 5

Fig. 4. The patient at the age of eight The exophthalmus as well as the as mmetrical k ll are l noticed

Fig 5. The patient at the age of seventeen. Not the considerable asymmetry of he face The ri ht half is less dev loped han the lef

recurrence of his diabetes insipidus, he was admitted to the Medical Department of the Vänersborg Central Hospital in December 1960.

On admission, the following observations were made. The boy was somewhat feeble. His length was 163 cm and his weight 47 kg. The face was asymmetrical. The right half was less developed than the left. A moderate hydrocephalus could be noticed. The circumference of the skull was 56,5 cm. One could also observe a slight exophthalmus and a divergent strabismus. The teeth were in a very bad condition. They were all decayed by caries and very irregularly placed. There was no real occlusive contact between the teeth of the upper jaw and those of the lower jaw. N skeleton changes could be palpated in earlier affected places.

The boy had radiological surveys of his entire skeleton. A pronounced asymmetry of the skull and an hydrocephalus shape could be noticed, but no defects or other traces f earlier observed hanges. Nothing was found of earlier processes in extremities or ribs.

Laboratory findings: Hemoglobin 95% (15.. g%). Erythrocytes 4.8 millions. Leukocytes 4800 (segmented neutrophils 56%, eosinophils 7 ..., lymphocytes 31%, monocytes 6%) Plat lets 200 000 per mm³. The bleeding time was minutes, and the coagulation time was 5 minutes. The cholesterol in the blood serum was 210 mg%. The verage amount of urine in 24 hours was 700–1600 g. Specific gravity 1 007. Chlorides in urine were 20 mEq/litre.

Discussion

This case shows a pathological picture that in it initial phase fulfils Siwe s eight criteria for the diagnosis of Letterer–Siwe disease [3]. In a later phase the patient shows a classical picture of Hand Schuller–Christian disease. Accordingly this case support Wallgren hypothesis of 1940 very well.

In 1954 Lightwood [3] reported 6 cases of recovery from Letterer–Siwe disease. The oldest of these cases was then 6 years old. These patients had all been given antibiotic treatment for some time. A few cases with just as favourable course have since been described. These patients have also been given antibiotic treatment. Before 1945 the disease was always considered to be fatal. This was probably due to the fact that previously the secondary infections, to which these patients are unusually susceptible could not be controlled. If this hypothesis is correct some of the patients who survived the first and certainly the hardest years ought now to be of the same age as our patient. His case is probably only an example of how the development of Letterer–Siwe disease may turn out in the long run.

Summary

A case of non-lipoid granulomatosis, which has been followed up for 15 years, is described. The malady begins as Letterer–Siwe disease. Later the patient develops classical Hand–Schüller–Christian disease. The connection between these two pathological pictures is pointed out. The importance of antibiotic treatment to the nowadays somewhat improved prognosis is discussed.

Acknowledgements

I am indebted to Dr G Edgren t the Halmstad Central Hospital for his help with data from the time he attended the patient, and to Dr O Gröntoft and Dr B. Jennische t the Vänersborg Central Hospital for thei help with the illustrations.

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Centrallasarettet
Vänersborg
Sweden

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CASE REPORT

Anomalous Inferior Vena Cava with Azygous and Hemiazygous Continuation

by AKE BRODELIUS BENGT W JOHANSSON and JAN SIEVERS

From the Roentgenological Department and the Cardiological Laboratory Department of Medicine, General Hospital, Malmö Sweden

Absence of the superior part of the in ferior vena cava is a rare condition which was first found at autopsy The first reports go as far back as the middle of the 10th century [Dorsch, 1858]

Pleasants [16] found an absence of the proximal part of the inferior vena cava and a wide azygous vein in an 18-year-old patient In 1947 Taussig reported one case of this anomaly [18] It was combined with total situs inversus and a biloculate heart, pulmonary stenosis and a left aortic arch. The diagnosis was made t utopsy

Effler *et al.* [11] described a case in which they found at thoracotomy a large "azygous vein which was ligated. At autopsy it was found to be an azygous vein draining the inferior vena cava

Not until heart catheterization and angiocardiography were used routinely in the diagnosis of heart disease was the first ante-mortem diagnosis of this condition reported.

Stackelberg *et al.* [17] described one case with no other anomalies. However these cases are often combined with other congenital cardiovascular lesions. The case reported by Levinson *et al* [15] showed a total transposition of the pulmonary veins. A persistent left superior vena cava and an atrial septal defect was found in one of the cases described by Stackelberg *et al* [17]. Campbell *et al* [7] and Anderson *et al* [ ] described cases in which the venous lesion was combined with other venous anomalies and a biloculate heart. One case with persistent left superior vena cava and absence of the right superior vena cava combined with a tetralogy of Fallot and another case with ventricular septal defect and persistent left superior vena cava were published by Downing [9]. A case with many congenital lesions, including among other things, a trilocu late heart pulmonary venous drainage into the portal vein, persistent left superior vena cava and a patent ductus arteriosus was reported by Druepple [10]. Grover [1] reviewed the literature and described a case which was combined with a patent ductus arteriosus and other heart anoma lies. Another case was reported by Latimer and Virden [14]. Kjellberg *et al* [13] discussed the embryology and described some simila cases. Recently Anderson *et al*



Fig. 1 Case 1 Frontal view of the heart Not the density t the position of the normal junction of the superior vena cava and the right trium.



Fig _ Case 1 Contrast injection at the level of the diaphragm Lateral view The big vessel coming from the inferior part of the bod empties l to the superior ena cava.

[ ] reported 15 new cases and published an extensive review of the literature

Some time ago we had the opportunity to tudy one case with an azygous vein and another with a hemiazygous vein draining the inferior vena cava which was atretic

Case 1 A 15-yea -old girl, born 1945 with moderat cardiac ymptoms such as dyspnea n exertion and light cyanosis f her lips at work H r symptoms had inten ified l ring the last few years and he had not taken part in gymnastics. She was no squatter Her mother ha a dystrophia myotonica with subject ve symptoms beginning bout 10 ears fter the pregnancy whicl was uneventful.

The physical xaminat on in 1961 revealed a well-developed and well nourished girl with moderat cyanos of her nail and poss bly a slight clubbing of her fingers The bl d pressure wa 1?0 80 mm Hg There wa systolic murmur o er the entire precordium w th maximum intensity grade IV in the left second interspace A thrill wa als felt at this ar There wa a slight diast lic mur mur over the base No signs f cardiac de compensation were bserved.

The lectrocardiogram showed n bl rhythm and a left is leviation with n signs of left or right ventricular hypertrophy

An X-ray of the heart revealed total heart volume of 730 ml corresponding t 480 ml per square metre f bod surface with enlargement of the left atrium nd th right entricle There w an increased as cularization of the lungs and a rounded lens ty to the right in the perior medi stinum (Fig 1)

C theterization wa made the right saphenous ein. The lent catheter passed through a es behind the heart nt the s perior ena cava and from here d wn t the right atri m, where the o gen content w found to be greater than n the ena ca a.

Contrast medium w injected int the an mal s ein at the le l f the diaph ragm. It passed through the led nd the heart and int the superior ena (Fig

and then went into a large common atrium; no atrial septum was found. Both ventricles were filled simultaneously as were the aorta and the pulmonary artery

Another catheterization was made from the left cubital vein. No signs of a ventricular septal defect were found. Nor did an angiocardiography with the tip of the catheter in the left ventricle show any communication between the right and the left ventricle The pressure in the right ventricle wa mod erately increased (50–30/10–2 mm Hg). No pulmonary hypertension was found (10/11 mm Hg) and the atrial pressure was also normal.

The angiocardiographies and a venography with a simultaneous contrast injection into both femoral veins showed that the superior part of the inferior vena cava wa lacking and that the azygous vein drained the lower part f the body The hepatic veins confluenced to a very short common trunk and emptied into the right atrium.

The girl is myopic and left-handed, but, besides the cardiovascular malformations, no ther congenital anomalies were found

Case — Girl born in October 1960. Preg nancy and delivery were uneventful. She was not cyanotic at rest but she became blue when she cried. She was dyspneic at rest At an age f 10 months she had already been hospitalized three times, because of acut bronchitis, possibly combined with bronchopneumonia. Her weight gain was less than normal.

Physical examination when the patient was 8 months old revealed lightly cyanotic and dyspnea hild without clubbing of her fingers. There was pansystolic murmur over the entire precordium with maximal intensity grade IV in the left second and third interspace N diastolic murmur was udible The femoral pulsations were normal. The liver was palpable 4 cm below the right costal margin.

The lectrocardiogram showed right entri cular hypertroph An X ray f the chest showed a ery enlarged heart and an in creased vascularization f the lungs (Fig 3)

At the catheterization which was made

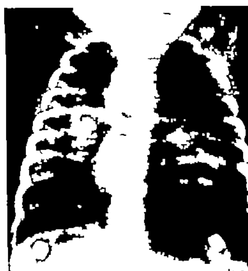


Fig. 3. Case — Frontal view of the heart



Fig 4. Case — Contrast injection at he level of he diaphragm Lateral view The big vessel coming from the inferior part of he bod empties in the superior ena ca a.

through the right saphenous vein it was never possible to reach the right atrium.

The angiocardiography (*Fig. 4*) revealed that the catheter was situated in an anomalous vein on the left side of the spine. This vein, probably the hemiazygous vein emptied into a left-sided superior vena cava, which passed into a big common atrium in which no septum was visible The contrast passed simultaneously into the pulmonary artery and into a right-sided aorta There was a good retrograde filling of the liver veins, but the inferior vena cava was *not* visualized. There was a malformation of the liver veins with two main stems, one from the right and one from the left liver lobe which was much bigger than normal. Besides the cardiovascular and hepatic findings there were no congenital malformations.

Comments

The development of the inferior vena cava during fetal life is very complicated and it is conceivable that malformations appear The inferior vena cava comprises the inferior part of the right inferior cardinal vein, the right hand part of the anastomosis between the two inferior cardinal veins the primitive inferior vena cava and the superior part of the right vena revehens (Fig 5) In the present cases there

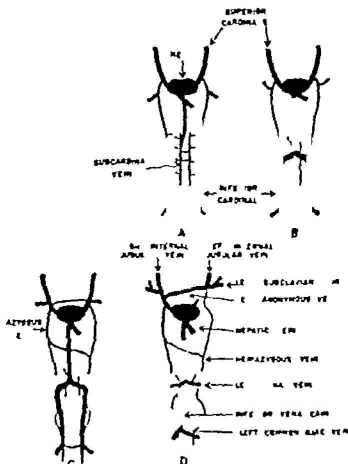


Fig 5. Different stages in the embryological development of the venous system Partly modified from Hroma (19)

seems to be a disturbance in the development of the three superior parts of the inferior vena cava mentioned above. This resulted in a persistence of the inferior cardinal vein as a large azygous and hemiazygous vein, respectively draining the inferior part of the inferior vena cava directly into the superior vena cava.

This anomaly has often been called "absence of the inferior vena cava" which may be seen from Fig. 5 to be incorrect. As has been proposed by Anderson *et al.* [3] a better name would be "anomalous inferior vena cava with azygous continuation".

This anomaly is most often combined with other cardiovascular malformations, as was the case in the present patients. One of the patients reported by Stackelberg *et al.* [17] is the only subject in recent reports who had no other complicating cardiovascular malformations. Downing [9] pointed out that in his cases he had seen a rounded density in the superior mediastinum which projected to the right at the position of the normal junction of the superior vena cava and the right atrium. This represents the dilated azygous vein and was also noted in the present Case 1.

Summary

Two cases are described with absence of the superior part of the inferior vena cava. The cases were combined with a trilocular heart (absence of the interatrial septum). Furthermore one of the cases had a left sided superior vena cava, a right-sided aorta and a malformation of the liver veins. The embryological development of the inferior vena cava is considered.

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Medical Department
Malmö Allmänna Sjukhus
Malmö
Sweden

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CASE REPORT

Chromosomal Translocation in a Mongoloid Girl with Some Atypical Features[1]

by K. H. GUSTAVSON

From the Institute for Medical Genetics, University of Uppsala, Sweden

In 1956 Tjio & Levan [17] established that the normal number of human chromosomes was 46 Most patients with mongolism have 47 chromosomes [2, 11 13] and the extra chromosome[2] is generally considered to be no 1 [2]. There is, however a small group of mongoloid patients having chromosomal variations other than that of trisomy for chromosome no . 1. The present report concerns a mongoloid patient with some atypical features who was shown, on cytological analysis to have a karyotype with 46 chromosomes including a probable 1/22 translocation.

Case Record

F mily history The patient parents were married in 1955. N cases of mongolism, malformation, mental retardation or other relevant conditions had been recorded among their near relat es.

Extens pulmonary sarcoidosis had been discovered in the father in 1950 and, in the succeeding ten years, he had had repeated chest X-rays. In 1957 following a complaint of sterility two seminal specimen from the father were examined at the Sterility La boratory Sabbatsberg Hospital, Stockholm, by Dr O.-G Lagergren, using the standard method of the laboratory [9]. Volume f seminal fluid, sperm count per ml, and motl lity of the spermatozoa were within normal limits. Differential counts, based on exa mination of 400 spermatozoa by phase contrast microscopy showed the presence of bout 50% of morphologically abnormal forms.

The mother had no history of serious ill ness or bortions. In 1958 he gave birth t a boy whose subsequent health and development have been normal. Her second preg nancy was uneventful. At this time the mother was 30 and the father 40 years old.

Description of the patient. L.T., a girl, was born by an uncomplicated breech delivery one month prematurely on May 5 1960. Her birth weight was 2600 g, height 47 cm and head circumference 32 cm. No neonatal complications were encountered

The patient was first referred for medical investigation at the age f ive months, when she was admitted t the Samariten Hospital for Children in Stockholm, following repea ted upper respiratory tract infections and an episode of acute gastro-enteritis. Her clinical picture at this time was somewhat sugges t ve of mongolism and a skin biopsy was taken for hromosome analysis.

Five months later she was admitted t the

[1] This investigation is part of research programme aided by grants Prof. J. A. Böök from the Foundations Fund for Research in Psychiatry he Swedish Medical Research Council, he Swedish Atomic Research Council, the International Atomic Energy Agency and the United States A omic Energy Commiss on.

[2] The Denver nomenclature of human mitotic chromosomes has been used consistently in this paper (*Lancet* 1063-1065, 1960).



Fig. 1. Roentgenogram of the patient's pelvis.

TABLE 1. *Summary of clinical investigation*

X-ray examination	
Skull	
Fontanelles and sutures	Normal for 10 months
Base	Normal
Facial bone structure	Normal
Nasal bones	Normal
Intracranial calcification	Nil
Skeleton	
Ossification centres	Normal for 10 month
Fifth finger phalanges	N[illegible] def[illegible]ty
Pel[illegible] (Fig. 1)	Normal
Iliac index	
Heart and lungs	Normal
Electrocardiogram	Normal
Electroencephalogram	Normal
Gesell Test	
Motor development	Equivalent to [illegible] child [illegible] [illegible] month
Adaptive and social development	Equivalent t[illegible] child of eight month

Laboratory findings	
Haemoglobin	Normal
Red cell count	Normal
White cell count	3700 cmm
Differential count	Normal
Bone marrow	Normal
Fasting blood sugar	91 mg 100 ml
Protein bound iodine	5.2 µg 100 ml
Serum protein	6.6 g 100 ml
Serum electrophoretic pattern	Normal
Wassermann reaction	Negative
Serological test for toxoplasmosis	Neg[illegible]
Urinalysis for:	
Protein	Negative
Abnormal sugars	Negative
Amino acid	Negative
Phenylpyruvic acid	Negative
Sediment	Normal



Fig. 2 a.



Fig. 2 b

Fig. 2 and b. The 12-month-old mongoloid girl.

Paediatric Clinic, Karolinska Sjukhuset Stockholm, because of dysphagia and suspected developmental retardation. She was observed to be rather small for her age. On physical examination slight muscular hypotonia and joint hyperflexibility were noted. There was no evidence f congenital heart disease. Examination f ears, nose and throat revealed normal conditions. Peripheral nonphysiological pigmentation f both fundi was observed on ophthalmoscopic examination. The results of special investigations are summarized in T ble 1

On physical examination in May 1961 (K. H Gustavson), the patient was once more noted to be somewhat small for her ge. Her height was 68 cm and her weight 6000 g. Craniometry ga e the following results cir cumference 44 cm (normal for her age) length 13.6 cm, breadth 10.. cm and cephalic index 75.

She had slightly oblique palpebral fissures, slight bilateral epicanthus and a flat nose bridge (Fig)

The upper helix of the right ear was over lapping, so that the margin formed a right angle with the descending part f the helix (Fig. 2b) This anomaly is often seen in mon golism. The configuration of the ears was otherwise normal. Her tongue was f normal size with no evidence f protrusion, fissures or papillary hypertrophy She had only two lower central incisors, both showing irregular alignment.

Her hands were relatively short and a four finger line was present on the left hand. The little fingers were normal in size and shape. Dermal ridge patterns of the hands were typically mongoloid, with a maximal atd angle f 90 on the right hand and 103 on the left. The feet were somewhat short but there was no unusual gap between the first and second toes.

Muscular tone was slightly decreased and some joint hyperflexibility was noted. The configurations f the thorax, bdomen and external genitalia were normal. N signs of congenital heart disease were elicited and there was no persistence of primitive reflexes Routine physical and neurological examination failed t reveal any further abnormalities.

Cytological Observations

Analysis of the patient's chromosomes was based on the study of cell cultures derived from one skin and one bone marrow biopsy. From each biopsy material four primary cell cultures and their subcultures were examined. The technique developed in this laboratory [4] was used throughout.

Chromosome studies on the parents were carried out on cultures derived from peripheral blood by a modification of the technique of Moorhead *et al.* [14].

The results of these analyses have been summarized in Table [illegible]. Deviations shown in the table are within the limits of those usually encountered in the use of current cytological procedures.

The cell cultures from the patient allowed chromosome counts to be made in 110 apparently undamaged cells in mitotic metaphase together with detailed analysis of [illegible] cells with the aid of enlarged photomicrographs. The chromosome number was 46. There were, however, only three short acrocentric chromosomes of group 21–22 instead of the normal four. The odd small acrocentric chromosome was tentatively identified as a no. 22 because of its somewhat smaller size. Furthermore, only two of the three short acrocentric chromosomes showed clear satellites.

Seven chromosomes were found in group 16–18 instead of the six normally present. The extra chromosome, which was metacentric, had almost the same length as no. 18 but a different centromere position. The karyotype is exemplified in Fig. 3.

In an attempt to identify the individual

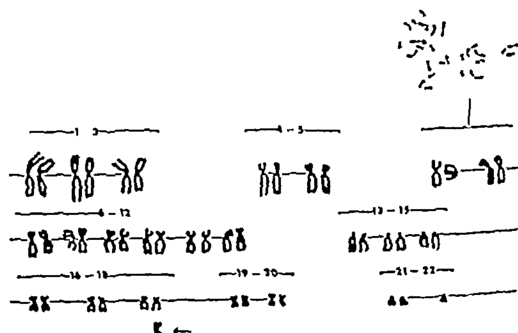


Fig. 2. Karyotype of the patient. 46 chromosomes, [illegible] an arrow. This chromosome is assumed to have originated through [illegible] and [illegible]

TABLE * *Summary of chromosome analyses of the patient and her parents*

Origin of cultured cells	Chromosome counts 45	46	47	Total number of analysed cells	Karyotype interpretation
Patient, skin		85		90	Translocation 1/22
Patient, bone marrow	1	18	1	*0	Translocation 1/22
Mother blood	1	13	1	15	Normal
F ther blood	1	14		15	Normal

chromosomes, the relative lengths and the arm ratios were calculated from measure ments of enlarged photomicrographs. In this way ten cells were analysed. The relative length of the extra chromosome was *7 as compared with 28 for no. 18 and 24 for no 19 The arm ratios were 2.4 and 1._ for nos. 18 and 19 respectively and 1 1 for the odd chromosome.

Typical sex chromatin was found in 45–55% of the interphase nuclei of cul tured skin and oral mucosa cells. Analysis of 15 cells from each parent showed normal chromosom numbers and karyotypes

While several explanations of the karyotype of this patient are theoretically possible the following interpretations ppear most likely

(1) The extra metacentric chromosome has arisen by a reciprocal translocation between chromosome no 1 and a chromosome no 22.

(*) The additional metacentric chromosome is homologous to one of the chromosomes in group 16–18

The first possibility seems to be the more likely one on morphological grounds The length of the short arms of the extra chromosome is the same as that of the long arms of chromosome no 22 and the long arms of the extra chromosome have the same length as the long arms of no *1 The frequent bservation of associations and attractions between the string parts of the satellited chromosomes should also favour this explanation.

The fact that both the arm length and the centromere position of the extra chromosome are different from those of the chromosomes in group 16–18 argues against trisomy for one of the members of this group As the mean arm ratio of the odd metacentric chromosome differs from unity it is unlikely to be an isochromosome

Comments

It is universally agreed that mongolism is characterized by a combination of mental deficiency and several physical abnormalities There is however no general agreement about which particular features should be required for diagnosis.

The absence of strictly defined diagnostic criteria as well as the variations associated with age sometimes exclude the possibility of making a definite diagnosis. In patients with suspected mongolism however the diagnosis can now be con firmed or excluded by n analysis of their karyotype

In mongolism, the classical trisomy for

The relativ length is the length of the chromosome relative to he total length of haploid set containing the X chromosome. The arm ratio is the length of he longer arm relative t the length of the shorter one

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CASE REPORT

Meconium Ileus Equivalent in a 15 Year Old Patient with Mucoviscidosis

by KAJ GOTLIEB JENSEN

From Surgical Department F (Head: Professor Einar Thomsen), Bispebjerg Hospital, Copenhagen, Denmark

Since Hiatt & Wilson's [7] report in 1948 on eight surgically treated cases of meconium ileu in newborn babies, several papers have been published dealing with the surgical treatment of this condition. On the other hand only a few accounts are available on a similar phenomenon in patients past the neonatal period

Levy [8] in 1951 described a case of "in testinal obstruction" with "putty like consistency" of the small bowel content in a boy aged months, suffering from mucoviscidosis. Fischer [6] in 1954 and Birse [1] in 1956 published very similar cases of mucoviscidosis in patients aged 15 and 16 months respectively. Finally Brown *et al.* [3] recently described three patients with mucoviscidosis operated on for fecal retention. The oldest of these was 9 years

The very few accounts of the meconium ileus equivalent in young and older children justifies in our opinion the following report, the more so because the condition seems not to have been described before in adolescents

Case Report

The patient was a 15 year old boy. Since the age of 6 months his nutritional progress has been poor and he has had fatty voluminous light-coloured, loose stools. During the past few years he has also been troubled by cough and dyspnoea on exertion. He has been admitted several times to pediatric units, and since February 1958 following diagnosis of congenital fibrocystic disease of the pancreas he has been treated with pancreatin 10 g twice daily, and a well complete though slightly low fat diet.

During the past year he has the patient has had repeated attacks of colicky pain in the right side of the abdomen. Such attacks occasionally accompanied by vomiting, have increased in frequency during the past few months, and the patient has within the same period been treated with 0.5 mg Scopyl (scopolamine methyl nitrate) tablets up to three times daily.

On November 1960 the patient was admitted with increasingly severe right abdominal pain of 2 days' duration, accompanied by vomiting, temperature rise to about 38 C, and retention of flatus and faeces.

The physical examination showed an underweight boy, considerably undersized, in height corresponding to physical development to a child aged 11. There were no other evidences of chronic disease. The lips were mildly cyanotic. He had drumstick fingers and was highly emaciated. Temperature 3 C, pulse 9. The tongue was moist. Auscultation of the heart and lungs was normal. Abdomen distended without guarding. There was diffuse tenderness



Fig. 1. Survey radiogram of the abdomen, showing gas-distended small intestine loops.



Fig. 2. X-ray of the thorax, showing increased lung marking with scattered, fibrous, dense areas.

umbilical tenderness maximum at McBurney's point where there was also indirect tenderness. On rectal exploration the patient complained of great tenderness upwards to the right, where a soft resistance was felt. An abdominal flat film revealed scant colonic gas but gas-distended loops of small intestine with fluid levels (Fig. 1). X-ray of the thorax showed increased lung marking with scattered fibrous, dense areas (Fig. 2).

Operation

On suspicion of acute appendicitis laparotomy was done through a right, transrectal incision in the lower part of the abdomen. This revealed abundant slightly haemorrhagic peritoneal fluid but no pus. The appendix displayed no acute changes. The distal 1½ to 2 metres of the small intestine on the other hand was found to be moderately dilated, hyperthrophic somewhat cyanotic, and to have viscous, pasty and, in places, lumpy contents. The colon was collapsed and normal. Examination of the remaining abdominal contents showed no abnormalities, more particularly no unquestionable changes were palpable over the area of the pancreas. A double-barrelled, relieving ileostomy was performed 15 cm proximal to the ileocecal junction. The intestinal lumen was filled with a viscous, sticky brownish black mass, which could only be detached from the mucosa with tweezers. Through a Nelaton catheter introduced into both intestinal limbs, a pancreatin suspension consisting of 3 g pancreatin suspended in 40 ml of physiological saline was infused daily. The day after the first pancreatin infusion pasty brown, homogeneous faecal matter was discharged through the ileostomy. The patient's condition improved appreciably and the ileostomy functioned daily. Four weeks after admission the normal intestinal passage was re-established.

Histological examination (E. Arfmann) of a resected ileal section showed the mucosa of the small intestine to be excessively mucous producing with practically no villi. There were inflammatory changes, and haemofuscinosis in the muscular layer (Fig. 3).

The postoperative course was uneventful. From the fourth day after the operation there were daily evacuations of pasty normal-coloured faeces. The patient was dis-



Fig 3. Photomicrograph of preparation (haematoxylin-eosin staining) from the almost non dilated ileal mucosa with moderately dilated glandular t bules and greatly increased number of goblet cells.

harged in well being 6 weeks after admission on a f t free high calorie diet vitamin supplements, and pancreatin granules 15 g twice daily

Laboratory analyse

Hb 9 04 E.S.R. 19-64 mm B.P 115/70 mm Hg Urine no alb., no suga Micro n abnormal ty

Icteric index 8-4 (Meulengracht). Takata Ara 1.50-1.0 Thymol 0.01 0.04 Urinary bilin 1 80-1 160-0 Urinary diastase 1.0 (Fabricius Moller) Prothr bin. 100 Arterial blood Oxygen sat ration 90 pH 7.51; pCO_2 33 mm Hg; Bica bonat 8.0 mM/l ECG no abnormal t Culture f sputum. *Staphylococcus a r s* *trolyte measurement* chloride 116 mEq/l ... m 89 1 mEq/l.

TABLE I *Analysis of duodenal juice The nzyme co centrations have be d t m l milli en yme units pe litre (mEz l)*

	Amount ml	pH	Total CO mM/l	Am lase mEz/l	Lipase mEz/l	Trypsin, mEz/l	Ch motrypsin, mEz/l
Fasting	6	6 1	1 1	[illegible]	Immeasurabl little		0
30 minutes after meal	13	6.63	.3	6	Immeasurabl little	0	
1 hour after meal	33	.33	4 7	6	Immeasurabl little	[illegible]	[illegible]
1½ hours after meal	10	5.6	0 9	5	Immeasurably little		0
hours after meal	10	[illegible]	1 4	0	Immeasurabl little	Immeasura l l	0

The concentrations of lipase, amylase trypsin and chymotrypsin in duodenal juice were analysed after aspiration through a thin polyvinyl tube introduced into the duodenum under X-ray guidance. The analyses were carried out by Dr Helge Worning in the Central Laboratory Blegdamshospitalet Af ter aspiration f fasting juice a stimulating meal wa given, consisting f 45 g nutrimin plus 20 g glucose plus 300 g water Nutrimin contains 60% fat-free milk powder 37% vegetable oil, and 3% water The individual aspirates were drawn under liquid paraffin. By the methods employed for enzyme measurements the enzyme concentrations are determined in milli-enzyme units per litre [4 9 10, 11] (T ble 1). *Measurable amounts of enzymes were not demonstrable* in our patient except for small amounts of amylase.

Discussion

In the case reported here the *primary* diagnosis of mucoviscidosis can be regard ed as sufficiently verified by the clinical course of the disease, as well as by the results of the quantitative analyses of sweat for electrolytes and of duodenal juice for pancreati enzymes. According to Shwachman *et al* [12] a sodium concen tration in sweat exceeding 80 mEq/l or a chloride concentration exceeding 70 mEq/l is diagnostic of mucoviscidosis, the normal values for sodium and chloride in sweat being about 50 mEq/l and 32 mEq/l, respectively In our patient we found a sodium concentration of 88.1 mEq/l and *a chloride concentration of 116 mEq/l*. Furthermore no measurable quantities of *intestinal enzymes* were present in the duodenal juice except for amylase which may have been due to salivary contamination

On operation th only cause of the obstruction w seen to be meconium like viscou sticky mass which completely filled up the dilated intestinal lumen. This picture is in perfect agreement with the descriptions of intestinal obstruction described in children with fibrocystic disease beyond the neonatal period In addition, it offers such conspicuous points of resemblance to meconium ileus in newborns that we feel justified in charac terising the present case as well as the previously reported cases, as the equival *ent of this condition occurring in older age-*classes.

The histological examination of a resec ted ileal section revealed, in addition to a greatly increased number of goblet cells in the glandular epithelium (as was also demonstrated by Bodian [ ] and Zuelzer & Newton [13]) an almost non villous *intestinal* mucosa, a finding which is worth emphasizing as it has not been described previously Patho-anatomically the possibility cannot be definitely ex cluded that the demonstrated changes may be due to the making of the ileostomy and its function. On this account biopsies from higher intestinal sections would have been desirable but for technical reasons could not be performed in this case The question whether a specific phenomenon was present must therefore be left unanswered.

It is universally agreed that the obstruction seen in meconium ileus is the direct result of th bnormally increased compactness of the small-bowel content in consequence of the failure of pancreatic enzym action.

In all the cases reported in the literature of meconium-ileus-like obstruction in children past the neonatal period the patients were under pancreatin-substitution treatment. In two cases [1 6] the

intestinal obstruction is known to have developed in direct relation to a failing supply of pancreatin Our patient had been treated with pancreatin granules 10 g three times daily for _ years Theoretically the acute obstruction may be explained by assuming that the dosage had become gradually insufficient a the patient grew up with consequently an increasingly incomplete digestion of the intestinal contents and a correspondingly increased compactness of them cau ing the subileus-like attack which had troubled the patient during the previous year or so The atropine-related drug scopyl given to the patient for several month because of these abdominal cases added to the in spissation of th intestinal content and had thus been the direct cause of the acute obstruction

On these grounds there may be reason to warn against administration of atropine or related preparations to patient suffering from mucoviscidosi

Summary

An account i given of a 1-y ar-ol male with mucoviscidosi operated on for ileus caused by viscous meconium-like small bowel content Ileost my wa performed, through which the patient w treated by pancreatin infu ion which had a prompt softening and homogenizing effect on the intestinal content A normal intestinal passage wa subsequently re established.

Histological examination showed the ileal mucosa to have practically no villi and a greatly increased number of goblet cell in the glandular epithelium remin scent of the condition in colonic epithelium

The fact that the patient had been given scopyl an atropine-related drug for some length of time ha been uggested as th direct releasing cause a thi may have further inspissated th in ufficiently di gested intestinal content

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PROGRESS IN PEDIATRICS

Acute Respiratory Illness in Children

A Combined Bacteriological and Virological Study

by GÖRAN STERNER and GÖSTA TUNEVALL

From the Children's Hospital Samariten and the Central Bacteriological Laboratory of Stockholm City

In some studies of recent years materials of acute respiratory disease in children have been analyzed with respect to the incidences of several types of respiratory virus and antibodies against these agents [1, 2, 3, 19]. As a growing number of virus types able to cause respiratory disease have been found, increasing proportions of these materials have been shown to harbour and react immunologically against such agents. The incidence of potentially pathogenic bacteria has also been investigated in the same groups, but the frequencies found have generally not differed from those observed in so-called normal materials [1, 2, 3, 7]. The primary or secondary aetiological significance of bacteria thus has not been possible to evaluate with any degree of safety. Groups of children with oto-rhinological infections have been studied sero-bacteriologically by Tunevall [15] in an attempt to state the part played by bacteria in such conditions, but no virological examination of these groups was done. The same methods were applied by Philipson to materials of non-diphtheritic croup in a combined virological and bacteriological study [9, 10].

The present study aims at elucidating by means of serological methods, the incidence of acute bacterial infection in a group of children with respiratory infections previously analyzed virologically chiefly for adenovirus infections.

Material

The children studied (0–15 years) have been in-patients or ambulantly treated at the Children's Hospital Samariten. They had at the first examination signs of acute respiratory disease and all of them have been examined serologically for adenovirus infection. Part of the material have been reported previously [6, 11].

Hospitalized children. This group comprises 143 children admitted from October 1954 to December 1957. All types of acute respiratory disease are represented, from simple rhinitis to severe bronchopneumonia. Only acute laryngo-tracheitis is rarely found within the group, as this condition is seldom referred to our hospital. As usual in acute respiratory disease symptoms and clinical findings were seldom restricted to any special part of the respiratory tract but several regions were affected. The material has therefore been divided into two groups only: those with bronchopneumonic processes ("pneumonia group") and those without ("non-pneumonic

group") This separation wa possible be cause in as many a 121 children chest X rays were performed (i.e. all cases with the slightest sign suggesting pulmonary in volvement such as cough or auscultatory *findings) Consequently ll 69 children allot* ted to the pneumonic group presented roentgenologic sign of pulmonary affection.

The paranasal cavities were X rayed in 93 hildren, 51 of which had alterations from slight swelling of the mucosa to massive obliteration of one or more sinuses. Purulent otiti occurred in six cases. Sinusiti and otitis were about a frequent within both of the two main groups.

O t patient Thi group comprises 3) children admitted from September 19 to January 1959 for acut respiratory disease For thi series only such hildren were selected a had been ill for less than eight days and had not been treated with hemo therapeutics or antibiotics. No pneumonic cases belong to this group

The age distribution within the two main groups wa the following

	Months		Years			
	0 3	4 11	1	3	8–15	Total
No pneumoni						
Hospitalized	3	9	13	4	5	74
Out patient			2	15	12	3
Pneumonia		3	6	32	6	69
Total	6	1		71	63	173

Method

V rological Method for virus isolation and serological test have been described in previous report (8, 1). In all cases, except 23 in the hospital group and 3 among the out pat ents, stool specimens were examined for cytopathic viru immediately on admission, or one of two days after the first visit to the out patient department In all cases complement fix tion (CF) tests for antibodies against adenov ru were performed with serum from the acut phase and with a new sample taken to 3 weeks later A few cases excreting adenovirus type 7 but showing no rise in CF ant body were als tested for neutralizing ant bodies

If any viru other than adenovirus had been isolated from the tool, test for neu tralizin ant bodies against the t pe of virus recovered were performed if suitable sera were available

During an influenza A epidemic in the late tumn of 19 complement fixation test again t influenza A and B were per formed on paired sera from ten hildren in each of the pneum nic and non pneumonic hospital groups and from all out patient

Test for cold aggl tinin against normal *human O-erythrocytes were made on ac* and convalescent phase serum especially taken for this purpose from 4 of the pneu monic ch ldren.

Bacteriological In the hospital group na sopharyngeal nose and throat swabs were taken a soon as possibl aft r admission and alw y before instalment of ant bacterial treatment In the out patient grou p, or y nasopharyngeal swabs were t ken, al t the first visit The samples ere cultured and potentially pathogenic bacteria verified accord g to con entional m thod

In all 30 out patient ar l 1?7 of the hospital group where after the sero logical tests sufficient serum d mo e ? remained, t trat ons of an t l es a nst potentially pathogenic bacter of the a passages were d ne When such an or ni m had been solated from a e the corre ponding ant b dy test wa performed in the f rst place

In the enumeration below th f und d ta concernin the sero ogical te ar gi en (1) The potentia y pa o enic ba t ria observed, (2) the corre ond g a t test used, (3) the ti res presen conside ed

as upper limits for normal variation as attained or exceeded by about 10% of an average adult population, (4) references to descriptions of the methods employed.

Pneumococcal Antipneumolysin (APn) 400 [16]
β-streptococcal Antistreptolysin (AS) 200 [4, 5]
Staphylococcus aureus Antistaphylolysin (ASta) 1 4 [8]
Haemophilus influenzae Complement fixing antibody (AHI) 20 [14]
Escherichia coli Anticolilysin (ACol) 500 [18]

The two samples from each patient were always assayed together in order t eliminat the effect of variation in the test systems. Therefore greater than twofold increase was considered t indicate that an antigenic stimulation had taken place in connection with the infectious condition studied, i.e. as far as the antilysin reactions were concerned. For complement fixation tests a fourfold increase was required. Also titre decreases of the same magnitude were taken as indicative of a recent antigenic influence, as showing that the first value had been significantly elevated above the child usual level.

In the 20 out-patients all five test could be performed with both serum samples. T what extent they could be carried out in the hospital group is seen below The draw back of the unavoidable incompleteness of the study is diminished by the fact that the tests corresponding to the cultural findings were carried out in the first place

	Number of cases	Number of cases tested for				
		APn	AS	ASta	AHI	ACol
Non-pneumonia	74	53	42	40	43	25
Pneumonia	69	60	56	48	55	40

	Number of cases	Number of different tests performed					
		5	4	3	2	1	0
Non-pneumonia	74	22	10	8	13	6	13
Pneumonia	69	27	8	9	8	5	3

Results

Virological

Table 1 presents the results of virus isolations All positive findings except that of a Coxsackie B5 infection were made among the hospitalized children. Adenovirus was isolated from 21 children 13 of whom had significant titre increases of complement fixing or neutralizing or both antibodies against adenovirus. Six children showed a significant rise in CF test against adenovirus, but adenovirus could not be isolated from the stools.

The child from whom poliovirus type 3 was isolated presented significant titre rise of complement fixing antibody during the disease and had thus probably fresh aparalytic polio ECHO virus type 9 was isolated from two children, but no antibody studies were performed in these cases. Of the two children with Coxsackie virus in their stools, the one with type B1 displayed a significant increase of homologous neutralizing antibody wherea the one excreting B5 virus showed no significant rise of such antibodies

To the information given in Table 1 it can further be added that serological evidence (fourfold or higher increase of CF antibody) was produced for fresh influenza B infection in two children with and one child without bronchopneumonia

TABLE 1. *Virus isolations from stool and significant (fourfold or more) rise of complement fixing (CF) antibody titre against adenovirus among 1 3 children with acute respiratory ill*

Virus	Without pneumonia: Isolation from stools	Without pneumonia: Significant rise in CF-reaction against adenovirus	With pneumonia: Isolation from stool	With pneumonia: Significant rise in CF-reaction against adenovirus
Adenovirus type		1		0
Adenovirus type 2	6	2	1	0
Adenovirus type 5	1	0	0	0
Adenovirus type 7	4	5		
Other adenovirus types	1	1	0	
Poliovirus type 2	1	0	0	0
Echovirus type 9		0	0	0
Coxsackie virus type B 1	1	0	1	
Coxsackie virus type B 5	1	0	0	0
No virus recovered	68	1	53	5
No isolation attempted	15	0	11	0
Total	101	11	69	

In addition one case with CF titre 32-64 and neutralization titre against adenovirus type 7 rising from t

At least a fourfold increase of cold agglutinins occurred in 6 of the 45 pneumonic children thus examined and an equally large decrease in additional 4 children.

Bacteriological

As antibiotic treatment before taking specimens for culture is likely to influence the frequency and type of bacteria the treated group is separated from the untreated one in the following Table 2. It should be mentioned also that only bacteria found in direct smear cultures on solid media are reported whereas findings after enriching procedures are left aside as probably irrelevant.

As is evident from Table no significant difference existed between the incidence of bacteria in the pneumonic group and that in the non-pneumonic one (3 isolates in 69 children versus 4 in 101). On the other hand a difference m es h n treated patients are compared with those not treated with antibiotics prior to sampling. In the untreated group gram positive cocci were recovered 4 times in 109 children (4) a a t 1 times in 64 children (2) in the treated group ($P \approx 0.0$). If only pneumonic children are counted the difference is especially marked (0.01 P 0.001).

On the other hand *H* *I* found in 10 of the 109 untreated (0) and in 0 of the 64 treated ones (14) It should be pointed out in this n that treatment is almost penicillin therapy.

Altogether 84 isolations were

TABLE 2. *Combined results of bacteriological cultures from pharyngeal and naso-pharyngeal swabs*

Findings are given in absolute figures and, in italics, as percentages of the number of children in each group. Pneumonic cases are separated from non pneumonic ones, as well as patient treated with antibiotics prior to sampling from those not treated. (From 10 children two different species were recovered.)

Group	Non pneumonia			Pneumonia			Together		
Antibiotic treatment	Not given	Given	Total	Not given	Given	Total	Not given	Given	Total
No. of cases	75	29	104	34	35	69	109	64	173
Pneumococci	8/*11*	4/*14*	12/*12*	8/*24*	3/*9*	11/*16*	16/*15*	7/*11*	23/*13*
β-streptococci	7/*9*	2/*7*	9/*9*	6/*18*	2/*6*	8/*1*	13/*12*	4/*6*	17/*10*
Staph. aureus	11/*15*	2/*7*	13/*13*	6/*18*	3/*9*	9 *13*	1 /*16*	5/*8*	22/*13*
H. influenzae	8/*11*	3/*17*	13/*13*	2/*6*	4/*11*	6/*9*	10/*9*	0 *14*	19/*11*
Coliforms	0	0	0	2/*6**	1/*3*	3/*4*	2/*2*	1/*2*	3/
Total	34/*45*	13/*45*	47/*45*	24/*71*	13/*37*	37/*54*	58,*53*	26/*41*	84/*49*
Patient with negative cultures	48/*64**	17/*59*	6_/*59*	13/*33*	24/*69*	37/*54*	55/*63*	41/*64*	99/*57*

* From one child in each of these two groups *B. pertussis* was isolated.

from 74 of the 173 children, 10 of whom harboured two different organisms.

The incidence of significant titre changes (increases and decreases) is presented in Table 3. The number of cases with increases versus decreases of the titres were: for APn 16/18, for AS 8/2, for ASta 3/2, for AHI 0/1 and for ACol 0/1. In this respect, no differences exist between treated and untreated patients or between pneumonic and non pneumonic. The only noteworthy fact emerging from Table 3 is the prominence of serological reaction against pneumococci.

TABLE 3. *Significant changes of antibody titres given in absolute figures and in italics as percentages of the number of children in each group*

Pneumonic cases are separated from non-pneumonic ones, as well as patients treated with antibiotics prior to first sampling from those not treated. (One child presented significant titre changes in three reactions, another one in two.)

Group	Non pneumonia			Pneumonia			Together		
Antibiotic treatment	Not given	Given	Total	Not given	Given	Total	Not given	Given	Total
No. of cases	75	29	104	34	35	69	109	64	173
Antipneumolysin	18/*20*	6/*21*	21/*20*	6/*18*	/*49*	13/*19*	21/*19*	13/*49*	34/*20*
Antistreptolysin	4/*5*	0	4/*4*	3/*9*	3/*9*	6 *9*	7/	3/*5*	10/*6*
Antistaphylolysin	2/*3*	0	/*2*	2/*6*	1 *3*	3,*4*	4/*4*	1/*2*	5/*3*
CF-antibody *H. influenzae*	1/*1*	0	1/*1*	0	0	0	1/*1*	0	1/*1*
Anticolilysin	1/*1*	0	1/*1*	0	0	0	1/*1*	0	1/*1*
Total	23/*31*	6/*21*	29 *28*	11/*32*	11/*31*	22/*3*	34/*31*	17/*27*	51/*29*

A presentation of the titre distributions for different antibody reactions is given in Fig 1 Here the anticolilysin titres are omitted a apparently non informative in thi group of children For comparison the distributions of antibody titres in different age groups in so-called normal material observed by Tunevall [15] are given.

In fairly good agreement with previous observations [15 16 17] the profiles for anti pneumolysin titres in the present material tend to move to the right (towards higher values) already from the first year of life whereas those of antistreptolysin and anti-staphylolysin do not show the same tendency until the fourth and more pronouncedly not until the ninth year of life As for the *H influenzae* antibodies the titres of the older children in our material are even lower than those of the so-called normal material of the same ages

Combi ed virological a d bact riological data

In Fig the combined result of the virological investigation are reported It seen that regardle of whether pneu moni or non pneumonic and wh ther treated bef re sampling or not the whole material can be divi led into three groups with regard to the laboratory findings. The first group con tituting from 3 to 43 of the subgroups (average 39) ha presented serological evidence of fresh infection with viru (31 cases 3 f whi h with reactions again t two ent and 15 cases with imult neou isolation of the agent in question) or w th bacteria (48 cases one of whi ich with react on a a n t two agent and cases w th is l tion of the correspondin bacterial pecies) In 11 cases (20) sign of fresh infection with both virus and bacteria were recorded

In the cases of the second group m ki g up from 14 to 41 of the subgroup (average 28) isolation of potentially pathogenic agent have been made b t no serological confirmation of any rela tionship to recent infection ha been obtained Viru was recovered in 9 cases bacteria in 41 6 of which double findings and 4 with simultaneou finding of viru

In the third group, containing from to 43 of the ubgroups (average 33) no findings were made

This mean that in bout one third f our material we could demon trat fresh infections with viru and or bacteria wherea in another third such infect n were only suggested but n t serologically verified and the la t third of the cases ga complet ly negative finding

Among other observations in our m terial a few may be mentioned a cert inly not original but fitting in w ll with present concept Adenoviru wa f und most ften in non pneumoni cases and wh n recovered in pneumonic children it accompanied in most of th cases by bac teria Cold agglutinin were f und f r only in pneumonic children and ere lemonstrated f irly often in th absence of bacterial findin s

Di cu i n

The isolation of a p tent lly path agent in the n le case l es n t l f pro a a sal n f nee f th agent part ul rly not in inf ct n f t respiratory tract where th r m h ent re dten rec ered m l The can le he l tl ontif c al t

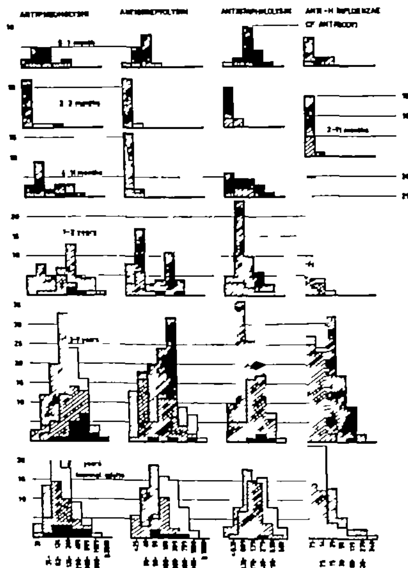


Fig. 1. Distribution in different age groups of antibody titres within "normal material" previously observed by Tunevall [18], and of the highest of two titres observed in every child of the present material of acute respiratory illnesses. Normal material: shaded columns. The present material of respiratory illnesses: white columns (sparsely shaded when coinciding with the former). Number of children with significant titre changes and thus shown to suffer from fresh infection with the corresponding agent: marked in black. Figures in the margins denote number of children. The normal distributions combined with the 6–15 years group have been recorded in adults.

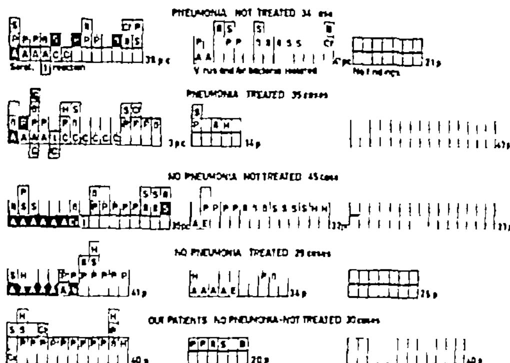


Fig. Isolations of irus and bacteria, nd significant antibody titre changes in the en ire ma erial of 173 hildren with acut respiratory disease. E ery patient is represented by vertical set of squ. Virologic findings below the double horizontal line, bacteriologic findings ab ove. White sign in bl k field = isolation significant titre change. Black sign in shaded field significant t re change alone. Black sign in whit field isolation lone. *A* adenovirus, *C* Coxsackie irus, *E* ECHO irus, *I* = influenza irus, *Po* polio irus, *C* cold agglutinins, *P* pneumococci, *β* β-strept cocci, *S* = Staphylococcus aureus, *H* *Haemoph lus* flue zae, *Cl* coliform bacteria, *B* *B. fetid.* pert sis.

after the acute infection. Th demonstration of a ignificant change in titre of an antibody again t the isolated agent the correlation in time between infection and the d sease may be establi hed but thi i not equivalent to a causal relation hip. On the other hand if no titre increase of antibodies again t any other agent known to produce respiratory illness i found the aetiologic ignif cance of the isolated agent is further trengthened. Such con idera tions have often been xpressed in con nection with virologic tudies but ha e been largely neglected in bacteriological work.

The present investigat on wa perf rmed in order to exam ne t what xtent it possible within a heterogene material of respiratory illness in ch ldren to l k the acut condi tion t th presence of p tentially pathogen ent viral or bacterial ones by me of sero ogical metho l.

When d scu ing th result of th tud it hould be tressed th t th material w collected during peri d f several years inv lvin pidemics of er peri l w t h t incidence f t p l pneumo adeno iru infection ECHO 9 infect ns nd influenza A

Further some unfavourable conditions are likely to have diminished the chances of demonstrating fresh infections within the material. It seems possible to eliminate some of them in future studies of this type. Thus new techniques for the isolation of more recently demonstrated types of respiratory virus, as well as the inclusion of such agents in the array of antigens used in the serological study are desirable. Taking specimens more than once for virologic and bacteriologic isolations and more than twice for antibody assays will, as will be shown in a subsequent study, increase the possibility of demonstrating pathogenic agents and immunologic reactions provoked by them. Further the selection of patients not treated antibacterially prior to sampling would certainly increase the recovery rates for bacteria and possibly also the frequency of significant antibody titre increases [13].

Two other disturbing circumstances are more difficult to eliminate, viz. the possibility that effective antibacterial treatment during the stay in the hospital may interfere with the immunologic response to demonstrated bacteria and, on the other hand, that nosocomial infections acquired after sampling for bacterial culture may provoke serological reactions which do not correspond to the isolation of the bacterial species in question. In both cases no correspondence between cultural and serological findings is likely to be found.

With consideration to the circumstances mentioned above this study can be seen only as a preliminary survey of the possibilities of connecting cases of acute respiratory illness to simultaneous infection with viral and bacterial agents known to produce such disease. Nevertheless, some observations of interest have been made. During periods when no epidemics predominate the aetiological conditions seem to be very complex, involving a considerable number of viral and bacterial agents. These may occur together in mixed infections with viral and one or more bacterial components. This complexity should be borne in mind, especially in connection with the clinical testing of new antibacterial agents.

Summary

One hundred and seventy-three cases of acute respiratory illness in children, with or without bronchopneumonia, have been analyzed with virologic and bacteriologic techniques, including serological methods. It was thereby possible to demonstrate fresh infections with virus and/or bacteria in one-third of the material (mixed infection in 20 %). In another third of the cases potentially pathogenic agents were isolated but serological evidence of their causing a fresh infection was lacking. From the remaining third no findings were made. Knowledge of the aetiological factors is essential for evaluating therapeutic effects of antibacterial drugs in acute respiratory illness.

Acknowledgement

The virus studies in this work were carried out in the virological department of the Central Bacteriological Laboratory (Head: A. Svedmyr) by L. Kjellén, Marianne Ohlson and G. von Zeipel. Their valuable assistance is gratefully acknowledged.

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Sweden

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SUMMARY OF SUPPLEMENTS

Long Term Prognosis in Juvenile Diabetes Mellitus

by YNGVE LARSSON and GÖRAN STERKY
with the collaboration of GUNNAR CHRISTIANSSON

(S pplement 130)

The long-term prognosis of juvenile dia betes was evaluated in a material com prising 168 cases with onset of diabetes during the first 16 years of life Of these there were 42 patients who had died, 1 from diabetic angiopathy and 1 from non vascular diseases. With the exception of 14 patients who died early the duration of diabetes was more than 15 years, with a mean duration of 1 years and a range of 16–33 years. The mean chronological age was 27 years, with a range of 18–40 years. Age at onset of diabetes was for 7 patients 0–5 years, for 60 patients 6–10 years and for 36 patients 11–15 years (Chapter I.)

The methods used at the follow up ex amination are described. The study in cluded complete physical, ophtalmological, cardiovascular renal and electro-ence-phalographic examinations. The lipids and proteins in the blood, and the urinary excretion of hormones were analyzed (Chapter II.)

Insulin was used by all patients. Two thirds of them took insulin once a day the remainder twice The range of insulin dosage wa from 20 to over 100 units In 45.8% the insulin need exceeded 60 units day Although all patients origi nally had received a so-called free diet treatment three types of dietary habits could be recorded, regulated normal diet (28 4%) free diet minus sugar (30.5%) and entirely unregulated free diet (32.1%) Among 1_5 living patients 80% had nor mal working capacity while 1_8% were wholly and _ partially disabled. (Chapter III.)

Data are given for height and weight In 9 men (1_9 %) and women (3.3%) the height was below the lower normal limit The mean height (for men 170._ cm and for women 161 0 cm) was significantly lower than for the non-diabetic population. Overweight was present in 4 men (5 7%) and 8 women (13.3 %) but the mean body weight was below standard weight for both sexes (for men −8.3 % and for women −3 4%). The body proportions were slightly abnormal in the men. The tendency towards short stature and thinness was thus more pronounced in the men than in the women. (Chapter IV)

A two-dimensional description of the blood pressure is presented. The 95 % lim-it for blood pressure were calculated from a Norwegian study of more than 4000 non-diabetic subjects in the age group _3–20 years The following values

were obtained: for men 160/95 and for women 150/90 mm Hg. Among living patients 12.5 % of the men and 29.6 % of the women exceeded these limits. Among patients who had died, most of them from nephropathy, hypertension had occurred in 75 %. Electrocardiograms were abnormal in 10.5 %. Roentgenological enlargement of the heart occurred in 10.3 %. (Chapter V.)

For each one of 82 hospitalized patients a mean blood-sugar was calculated. In 69.5 % it was below and in 30.5 % above 200 mg/100 ml. There was no relation between mean blood-sugar and type of diet. Continuous glycosuria was present in the majority of the cases. Hypercholesterolemia (above 300 mg/100 ml) was observed in 52.2 % and hyperlipemia (total lipids above 800 mg/100 ml) in 48.6 %. A relation was found to exist between the *duration of diabetes and increase in blood lipids* and also between hyperlipemia and chronological age. The ESR was increased in 37.9 % of the men and in [illegible] % of the women. Demonstrable signs of liver dysfunction were found only in a very few patients. NPN was increased in 19.5 %. (Chapter VI.)

The mortality from diabetic angiopathy declined with increasing duration of diabetes being 22, 13 and 0 % in the three duration classes. It increased with age at onset of diabetes being 0, 15 and 30 % in the three age-at-onset classes. There was no relation between mortality and chronological age. Cumulative mortality and cumulative death risk curves have been constructed. A formula is devised for the calculation of the total death risk, which was found to be 20.6 % for the whole material. The risk increased with age at onset, being 9, 20 and 35 % in the three age-at-onset classes. (Chapter VII.)

Retinopathy (R) and vascular calcifications (A) occurred in 81 % and nephropathy (N) in 50 % of the patients, deaths included. Subjective symptoms were present only in a minority of these cases however. There was no correlation between angiopathy and duration of diabetes but significant relations between angiopathy and age at onset were observed, in analogy to what was shown with regard to mortality. There was no connection between chronological age and R or N; for A, however, an increase was observed with age. No sex difference was noted as regards incidence of angiopathy. The occurrence of combined angiopathy was analyzed. 10 cases were entirely free from angiopathy, 23 had either R or A, 39 had two types of angiopathy (RA, RN or AN) and 85 displayed *symptoms of all three types* of angiopathy (RAN). Combined angiopathy showed no significant relation to duration, but there was a significant relation to age at onset and a probably significant relation to chronological age. There was no correlation between combined angiopathy and type of insulin treatment, dietary habits or degree of physical activity, and probably no correlation with blood sugar level or blood lipids. The course of angiopathy was studied during a 10-year period. Out of 100 cases R deteriorated in 63, was unchanged in 29 and improved in 8. In another group of 40 patients all of whom had been free from signs of angiopathy at the beginning of the 10 years, angiopathy had developed in [illegible] cases, but to a widely varying degree. It was observed that more severe forms of angiopathy tended to occur in patient

who had had a high cholesterol level at the first examination. The renal clearances of inulin, para-amino-hippuric acid, endogenous creatinine and glucose were determined in 78 patients. In cases without proteinuria the clearance values were within normal limits. In patients with proteinuria only inulin clearance was decreased. Thus, clearance tests were of little value for the early diagnosis of diabetic nephropathy. A significant correlation was found between inulin clearance and glucose-Tm. (Chapter VIII.)

The serum proteins were analyzed both by free and by paper electrophoresis. A high alpha$_2$-globulin was found in most patients. However this increase was significant only for cases with nephropathy (Chapter IX.)

There were 32 women in the material who had been pregnant in all 66 times. For these the total fetal and infant survival was 26.4 %. This low figure was probably due to lack of strict control during pregnancy. There were no signs of aggravation of angiopathy after pregnancy. (Chapter X.)

The urinary excretion of 17-ketosteroids was lower than normal, especially among the men. A similar tendency was observed with regard to the excretion of corticosteroids (17-OHCS). The excretion of oestrogens and pituitary gonadotropins may also have been somewhat lower than normal but the results do not permit of any definite conclusions. (Chapter XI.)

EEG studies on 80 patients 16–28 years of age with juvenile diabetes of more than 15 years duration showed pathological EEGs in 31 %, borderline findings in 29 % and normal EEGs in 40 % of the cases. Pathological EEGs were more common in women than in men. No correlation was found between abnormal EEG and other factors such as age at onset, age at the time of study, duration of diabetes, blood sugar level at EEG examination, serum lipid values, degree of diabetic control or appearance of angiopathy. The results of the investigation are in agreement with the hypothesis that EEG abnormality in diabetic patients might be due to constitutional factors. (Chapter XII.)

In the discussion it is pointed out with regard to the composition of the material, that it is a purely juvenile series, that all patients could be traced at the follow-up examination, and that the series is larger than most similar series, previously published. From the point of view of treatment and control it is also a uniform material. The favourable influence of an early onset of diabetes on mortality and angiopathy is assumed to be connected with the length of the post-puberty period, for during puberty postulated atherogenic factors begin to be active. The relations between angiopathy and treatment are discussed. Even if it remains doubtful whether careful diabetic control can improve to any considerable extent the prognosis of the disease, a more strict diabetic control is considered to be the therapeutic alternative which has to be tested more thoroughly in the treatment of juvenile diabetes. The criteria for such control are described. Instruction of patients is an especially important part of the treatment. The continuity of pediatric supervision should be maintained during puberty and adolescence into adult age. In addition to an intensified treatment it is considered important to study the possible risk factors which, in some patients give rise to

a more malignant course than in others. Several such risk factors humoral and clinical, are mentioned, blood lipids, blood ketones insulin antagonists hereditary disposition to vascular disease, etc It is concluded that *more effective means* are needed for the prevention, as well as for the early diagnosis and treatment of diabetic vascular disease (Chapter XIII).

The Children of Swedish Nomad Lapps
A Study of their Health Growth and Development

by TORE MELLBIN

(Supplement 131)

The children of the nomad mountain Lapps in the northernmost part of Sweden differ from other Swedish children by belonging to another race group and by the nomad life resulting from the care of reindeer For this reason, growth, development and health have been investigated in all the 450 children from 7–14 years of age who during the years 1957 to 1960 were attending the six nomad boarding schools in the County of Norrbotten (Karesuando Lannavaara Jukkasjärvi, Gällivare Jokkmokk and Arjeplog) There are differences in both race and environment between children in the north and the south, *so that the results obtained have been described with the series divided* up according to the schools. Since the parents of a number of children in the southern schools have moved from the northern parts of the county to the present areas since about 1930 the series has also been divided up into three *ethnic groups* children of north Lapps living in the north (N) children of north Lapps living in the south (N_s) and children of south Lapps (S) By this means it has been possible to compare children of similar origin who have grown up in different environments.

In Chapter I the Lapps and their living conditions are briefly described. The series and the statistical methods are presented in Chapter II The social standard is reflected in the large number of children per family an average of 5.3 and in the high infant and child mortality 7 0% of live born children dying during the first year of life (Chapter III) It is remarkable that girls predominate among live born children in the northern districts while the ratio between boys and girls in the southern districts is the same as for the *rest of Sweden.*

Chapter IV describes the dietary habits among the Lapps. The breast feeding periods are very long 37 % of the children receiving breast milk for more than 1 months and 6 6 % for more than 18 months. The diet in the pre-school years was not examined in detail but is characterized by a high protein content The consumption of vitamin D by the children has previously

been unsatisfactory Differences in these respects between north and south indicate a higher living standard among the Lapps in the south. The diet at the nomad boarding schools was investigated in two ways, a survey of all the schools and a more detailed investigation in Karesuando The results show that the diet was very satisfactory

The Lapp children differ racially from the rest of the population and there are also differences between groups within the series (Chapter V). In order to get an idea of these differences, determinations of blood groups haptoglobin types and a series of qualitative anthropological traits were carried out. Blood group A_2 was found in 54% with a higher incidence among south Lapps, the C^w-gene in 25% of the children with a higher frequency among north Lapps. Only 5% of the children were Rh(D) negative. Haptoglobin type 1–1 wa found in 9%. Among the qualitative traits, there were north-south differences in nose shape and bility to roll the tongue

Investigations of the Lapp children's growth and development are described in Chapter VI The children's birth weights and lengths are much less than the corresponding values for the "Swedish" children used for comparison. On the other hand there are no differences between Lapp children born in northern and southern areas or children born during different periods of time From 7 to 14 years of age the body height is a great deal less in Lapp hildren than in "Swedish" children. The Lapp children in the northernmost schools re considerably shorter than those in the southernmost while the children in the other schools are intermediate A clear increase in body height was also found in children born 1950–1953 compared with those born 1942–1946 a difference most pronounced in the far north. Body weight in relation to height shows that Lapp children are heavier than "Swedish" children of the corresponding ages The results found are supported by investigations of a series of Lapp children born 1927–1943 These children are both shorter and heavier than the children in the present nomad school series. Investigations of puberty development show that children in the southern areas develop earlier than in the northern. The differences in growth and development have been put in relation to the genetic factors examined. It was found that hereditary conditions play an undoubted part but the results show especially the great importance of environment. However the latter xerts its influence during the time before the beginning of school. The very good school environment did not affect the children's development in this investigation.

Congenital malformations (Chapter VII) were observed among the Lapp children and especially clubfoot, which occurred in 1.8% of the boys and congenital dislocation of the hip which was found in 4 7 of the girls.

The clinical examinations (Chapter VIII) showed a comparatively high incidence of enlarged epiphyses, the result of rickets during the first years f life Curved lower legs were found in 61% of the younger children and in 48% of the older The frequencies and correlation coefficients indicat that these findings are connected with genetic factors and do not result from exogenous factors

or deficiencies. Examinations of the children's hearing showed a high incidence of hearing impairment especially in the northernmost schools as a result of previous infections. Examination of the children's vision showed a high incidence of visual impairment, especially among those in Jokkmokk. The incidence of allergic disorders is low as shown by both the number of children with eczema and the results of intradermal tests with extract of reindeer epithelium. Roentgen examinations of the lungs showed no case of active tuberculosis and tuberculin tests showed that 37 % of the children in the total series were tuberculin negative and 67 % of the beginners.

The laboratory investigations showed comparatively low haemoglobin values with lower values in the southern schools and after some time at school. Examinations of sedimentation rate showed higher values after some time at school than at the beginning of school. The lower haemoglobin values and the higher sedimentation rates after some weeks at school are most likely explained by subclinical infections in the institutional environment. Haemoglobin electrophoresis did not show any haemoglobin anomalies. White blood count and differential count showed no notable results, except that 44 % of the children had 5 % of more eosinophil leucocytes. No obvious explanation of this fact could be found.

The incidence of parasites was low except for Oxyuris (Enterobius) vermicularis which was found in 41 % of the children. No child had *Ascaris lumbricoides*, *Taenia* or *Diphyllobothrium latum*. The investigations revealed no case of *Echinococcus granulosus* but one boy in the series was later operated for an echinococcus cyst.

BOOK REVIEWS

J Weissfeiler (Ed): The control f poliomyelitis by live poliovirus vaccine

Akademia Kiado, Budapest, 1961

This book deals with the results of an immense vaccination program in Russia Hungary and East Germany In 1959 and 1960 more than 90 million Russians and about 2½ million Hungarians were given the Sabin strains f poliovirus vaccine. During the "cold war It is consoling t read this volume on an immense joint effort f American and Russian scientists. The first chapter by Dr A. Sabin discusses the problems of vaccinating newborn children. Failure of the vaccine virus t multiply in some vaccinated newborns was found, even though 10–100 times the usual dose was used. In addition, in some vaccinated newborns antibodies did not develop, even though evidence f enteric virus reproduction was present and they were not resistant on refeeding On this basis Dr Sabin recommends that vaccination be postponed till 2 months f age However little data supporting this conclusion is presented in the report. The rest f the book are reports mainly by Russian and Hungarian workers on the immense vaccination program. The reports indicat that considerable decrease in the incidence f paralytic polio was caused by the vaccination and no case f paralytic polio due t the vaccine was reported. The reader gets the impression that the problem f polio vaccination is now solved and repeated statement occur that the vaccines are completely saf (The report seem t be written for political audience as well as for a scient fic one) The value of formalinized (killed) vaccines has been underestimated and the great differences in the qualit of these vaccines are not discussed. It is stressed that fter vaccination with live poliovirus vaccine there has been a very marked suppression of the circulation of live (wild) poliovirus. This has been observed even in Sweden where as yet only killed vaccine has been used on a large scale N one would, however deny that vaccination with live poliovirus vaccine represents an immense step forward and this book is an excellent proof f it

Rutger Lagercrantz, Stockholm

John Caffey Pediatric X Ray Diagnosis.

Year Book Medical Publishers Inc Chicago 1961 Price 32 dollars.

This well-known textbook, which is classic of current medical literature has now been issued in its fourth edition Material on 127 new items, richly illustrated with 644 pictures and drawings, comprising the advances in pediatric roentgen diagnosis since the previous edition, has been added With these additions most aspects of pediatrics amenable to roentgen diagnosis now presented and supported by figures drawings and diagrams of high quality Th reader is provided with an extended bibli graphy with no less than 450 new refere The fourth edition f "Pediatric X R Diagnosis continues to maint in th tion f ts predecessors as the most and comprehensive text book this field. Radiologists and pedia be grateful for the invaluable edition will give

H im G Ginott Group [illegible] Children. The Theory and [illegible] Therapy

McGraw Hill, New York

This book is intended [illegible] group therapy work [illegible]

offers a penetrating and well-grounded exposition of elementary matters such as group composition, play material, and therapy environment. More advanced problems, including the therapeutic process, the relation between patient and treatment, and the significance of limits in therapy are also dealt with The term "group therapy" has, in recent years, become a password in child psychiatry The author in his introduction states that attitudes towards group therapy have hanged, first because of scientific testing of its scope and theory and secondly its more realisti development to meet the increased demand for treatment. The literature cited in support of the first assertion is not impressive, and only general outlines are given. The author passes over the second point attempting instead to show that group therapy is superior to individual treatment H mentions certain cases more amenable to individual treatment but in truth many of these are serious cases not amenable to any form of treatment Group therapy he recommends mainly for "children who are withdrawn, immature phobic, or disorderly in behaviour" This is probably the weakest part of the book.

The material is presented in a readable form which ought to be useful not only to psychiatrists and psychologists, but also to pediatricians desiring reliable information on related fields of medicine The a thor avoids over-theorising and his therapeutic methods are characterised by a natural approach to children.

Lars Billing Stockholm

Franz Wurst, Hansjörg Wassertheurer and *Karla Kimeswenger* Entwickl ng und Umwelt des Landkindes (The Development and Environment of the Country Child).

Österreichischer Bundesverlag, Wien 1961 Price DM 52 50.

The authors of this book have made a very thorough medical, psychological and sociological study of the children in 40 rural, elementary and public schools in the *rather isolated Austrian province of Kärnten*. The data have been collected by the school doctors and their assistants and ha e then been processed on punched cards by modern statistical methods. The growth, the maturing process, the constitution, the test performances and various aberrations of behaviour are analyzed in the light of different anamnestical facts. The a thors present a thorough analysis of the effects of social conditions on the dev lopment of different psychosomatic perturbations—nail-biting, stuttering loss of ppetit incontinence and various st tes of anxiety Special attention has been paid to the study of environmental factors ruling the process of biological development. This book is not f solely medical interest but is also of great value t those interested in rural and general pediatric sociology It is, furthermore evident that the modern medico-sociological approach employ ed in this work will form the corner-stone of research into human ecology

The book, which is a result of balanced team work, contains 354 pages, is well illustrated and has a *fairly large* literature survey

Ola Wass Höbert Helsingfors

Acta Pædiatrica 51 367—368, May 1962

NEW BOOKS

Books received by the Acta Pædiatrica are acknowledged under this heading Selected books will be reviewed in subsequent issues as space permits.

Psychosomatic Aspects of Paediatrics R Macheith and J Sandler Pergamon Press. Oxford. 1961. Price 50s. net.

Die Gaumenmandel Darstellung der Biologie und Physiopathologie A. Fioretti. Georg Thieme. Stuttgart. 1961 Price DM 39·80.

Mental Retardation. Proceedings of the First International Medical Conference. P W Bowman and H V Mautner (Ed.). Grune & Stratton. New York. 1961.

Brain Injuries of the Newborn. P Schwartz. S. Karger Basel. 1961

XIII^ème Congrès de l'Association des Pédiatres de Langue Française F Bamatter & A. Mégevand (Ed.) Four volumes. S Karger Basel. 1961 Price SF 165:—

Die Pflege des gesunden und des kranken Kindes W Catel. Georg Thieme. Stuttgart 1961 Price. DM 42.—

Introduction to the Clinical Laboratory R. P MacFate Year Book Publishers, Inc. Chicago. 1961 Price $10:—

Group Psychotherapy with Children. H. G Ginott. McGraw Hill Publishing Company Ltd. London. 1961

Nutritio et Dieta Symposium. Parenterale Ernährung A. Hottinger & H. Berger (Ed.). S. Karger Basel. 1961 Price SF 16·—

Precocious Sexual Development. E. Thamdrup. Munksgaard. Copenhagen. 1961

Osteogenesis Imperfecta in Sweden. G Smårs in collaboration with R. Berfenstam. Scand. University Books. Stockholm. 1961

Manual of Pediatric Physical Diagnosis. Barness. 2d Ed. Year Book Publish. Chicago. 1961

Morbus Haemolyticus Neonatorum in ABO System K. Fischer Georg Thieme Stuttgart. 1961 Price DM 23.—

Child Mortality and Population Pressure in Jogjacarta. H. Timmer

The Control of Poliomyelitis by Live Poliovirus Vaccine J Weisfeiler (Ed.). Akademia Kiado. Budapest 1961

Contribution à la Biochémie des Oblatis Expérimentales J Christophe Editions Arscia. Bruxelles. 1961

The Nature of Sleep A Ciba Foundation Symposium J & A. Churchill Ltd London. 1961 Price 50s. net

Human Genetics. Brit Medical Bulletin The British Council. London. 1961

The M Intosh Era at Babies Hospital 1931–1960 A. Ashley Weech *et al.* (Ed.) Babies Hospital. New York. 1960

Lehrbuch der Kinderheilkunde. W Keller & A. Wiskott. Georg Thieme. Stuttgart. 1961 Price DM 78 —

Pregnancy and Diabetes Mellitus Lars Hagbard. Charles C Thomas. Springfield. 1961

European Symposium on Medical Enzymology Milano 1960 N Dioguardi. (Ed.). S Karger Basel. 1961 SF 70:—

The Neuroanatomic Basis for Clinical Neurology 2 ed. T L. Peele. McGraw Hill House London. 1961 Price £ 6. 4s.

Refraktometrie der Frauenmilch E Beitrag zur Kenntnis der Variabilität biologischer Vorgänge Gerh. Lindemann. Gustaf Fischer Verlag Jena. 1961 Price DM 12:35.

Pathology of the Fetus and Infant. Edith L. Potter 2nd ed. Year Book Publishers. Chicago. 1961. Price $22.—

Anorexia Nervosa. H Thomä. Verlag Hans Huber Bern. 1961 DM 16:50

Die Intersexualität. C. Overzier (Ed.) Georg Thieme Stuttgart. 1961 Price DM 119:—

Clinical Aspects of Nuclear Medicine Farr

offers a penetrating and well-grounded exposition of elementary matters such as group composition, play material, and therapy environment. More advanced problems, including the therapeutic process, the relation between patient and treatment and the significance of limits in therapy are also dealt with. The term "group therapy" has, in recent years, become a password in child psychiatry The author in his introduction states that attitudes towards group therapy have changed first because of scientific testing of its scope and theory and, secondly its more realistic development to meet the increased demand for treatment The literature cited in support of the first assertion is not impressive and only general outlines are given. The author passes over the second point, attempting instead to how that group therapy is superior to individual treatment He ment ons certain cases more amenable to individual treatment, but in truth, many of these are serious cases not amenable to any form of treatment. Group therapy he recommend mainly for "children who are withdrawn, immature phobic or disorderly in behaviour This is probably the weakest part of th book.

The material is presented in a readable form which ought to be useful not only to psychiatrist and psychologists, but also to pediatricians desiring reliable information on related fields of medicine The author avoids over-theorising and his therapeutic methods are characterised by a natural approach to children.

Lars Billing Stockholm

Franz Wurst Hansjörg Wassertheurer and Karla Kimeswenger Entwicklung und Umwelt des Landkindes (The Development and Environment of the Country Child)

Österreichischer Bundesverlag, Wien 1961 Price DM 5.50

The authors of this book have made very thorough, medical psychological and sociological study of the children in 40 rural, elementary and public schools in the rather isolated Austrian province of Kärnten. The data have been collected by the school doctors and their assistants and have then been processed on punched cards by modern statistical methods. The growth, the maturing process, the constitution, the test performances and various aberrations of behaviour are analyzed in the light of different anamnestical facts. The authors present a thorough analysis of the effects of social conditions on the development of different psychosomatic perturbations—nail-biting, stuttering, loss of appetite, incontinence and various states of anxiety Special ttention has been paid to the study of en ironmental factors ruling the process of biological development. This book is not of solely medical interest but is also of great value to those interested in rural and general pediatric sociology It is, furthermore, evident that the modern medico-sociological approach employed in this work will form the corner-stone of research into human ecology

The book, which is a result of balanced team-work, contains 354 pages, is well illustrated and ha a fairly large literature survey

Ole Wasz Höckert H lsingfors



Painting by David Tägtström

Wilhelm Wernstedt †

Wilhelm Wernstedt, professor emeritus of pediatrics at Karolinska Institutet died on April 9 196., aged almost 90 He had been a member of the Advisory Board since 1920 and had made frequent contributions to *Acta Pediatrica*.

Wernstedt studied medicine at the University of Uppsala 1890–1896 and subsequently at Karolinska Institutet, Stockholm, where he qualified in 1901 receiving his doctorate in 1906 From 1901 he was an assistant t the Pediatri Clinic of Allmänna Barnhuset, under Professor Oscar Medin and completed his practical training in pediatrics under Professor Jona Waern at the Lovisa Clinic in Stockholm 1910–1911 Wernstedt then became interested in bacteriology and infectious diseases While assistant at the Stat Bacteriological Laboratory he devoted his attention principally to field studies in poliomyelitis, which t that time occurred repeatedly in epidemic form in Sweden. He supplemented his income by private practice

In 1913 Wernstedt became assistant professor of pediatrics and chief of the newly built Flensburg Children s Hospital Malmö He returned to Stockholm as professor of pediatrics at Karolinska Institutet and chief of the Lovisa Children Hospital in 1921 Eleven years later he left this hospital to become chief of the Pediatric Clinic at Norrtull Hospital, where he remained until he became professor emeritus in 1937

Wernstedt extensive contributions to pediatric research were very much appreciated by contemporary pediatricians throughout Europe Pyloric stenosis, whi h he studied during almost the whole of his career w little known at the turn of the century Wernstedt published his first rticle on this disease in 1903 and the last in 1943 H showed that stenosis depended upon a combination of hyper

trophy and spastic contraction of the most distal portion of the stomach's musculature. The cause of these changes, which appear shortly after birth, remains unknown.

Studies on poliomyelitis, however, constituted Wernstedt's principal achievement. Little was then known about transmission and immunity, and his studies brought to light some important basic facts. In collaboration with Alfred Pettersson and Carl Kling, he proved, by experiments on monkeys, that the infectious agent was present on the mucous membranes of the respiratory and digestive tracts, not only in patients with paralytic poliomyelitis but also in abortive cases and in healthy persons living in epidemic areas. In his careful study of the poliomyelitis epidemics of 1911–1913 he advanced arguments in favour of the immunizing effect of polio infections, pointing out that new epidemics spared areas in which a previous epidemic had occurred. He also discovered a correlation between population density and extent of movement, on the one hand, and incidence of poliomyelitis on the other: the lower the morbidity the higher the population density and the greater the movement. These findings, which seemed at variance with the contagiousness of the disease, were explained by Wernstedt as resulting from general silent contact infections, followed by immunity. He also published new findings on the incubation period of poliomyelitis, and helped to clarify the clinical picture of the disease. These early epidemiological studies should be remembered at present, as they have largely been confirmed by recent virus studies and global vaccination experiments.

Another study worth recalling is that on tetany. Wernstedt was able to prove by clinical and experimental investigations that tetanic galvanic sensitivity was largely dependent on the salt content of cow milk whey (sodium and especially potassium ions produced an increase and calcium a decrease).

Wernstedt's other studies covered almost every problem of contemporary interest. He was the first to recommend and successfully use solid food in the treatment of habitual vomiting of infants. He showed that rumination in infancy was a psychosomatic illness, and that congenital stridor was a functional disorder.

A pioneer in Sweden in child psychiatry and psychology, he established a child guidance clinic at Norrtull's Hospital, and towards the end of his professorship began to publish scientific articles and popular pamphlets on mental health in infants and children. While professor *emeritus* he wrote a book on medical terminology of which the fourth edition appeared in 1960. Wernstedt, although then 88 years of age, did an excellent job of rewriting it.

Wilhelm Wernstedt was honorary secretary of the Swedish Pediatric Society 1907–1913, chairman, 1926–1927, and became an honorary member of the Society in 1932.

Arvid Wallgren

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From the Central Institute for Nutrition and Food Research T.N.O Utrecht and the Wilhelmina Children Hospital, Stat University of Utrecht the Netherlands

Diarrhoea Caused by Deficiency of Sugar Splitting Enzymes II

by H. A. WEIJERS and J H VAN DE KAMER

In a previous article [3] we proved that deficiencies in sugar-splitting enzymes may cause a chronic fermentative diarrhoea. This, of course does not imply that each fermentative diarrhoea is based on an enzyme deficiency for fermentative diarrhoeas may just as well be due to overloading the normal enzyme capacity or to a decreased enzyme activity (e.g by a deviation of the optimal pH) or to a reduction of the absorbing capacity of the intestine

A fermentative diarrhoea caused by a deficiency in sugar-splitting enzymes (lactase, invertase maltase or diastase) develops because non-absorbed disaccharides and/or starch are attacked by the intestinal flora, which reacts, among other things, with a marked production of lactic acid. In the first 24 to maximally 48 hours after the addition of a disaccharide to the diet, the non-absorbed disaccharides can still be demonstrated in the stools. After a maximum of 48 hours the non-absorbed part of the suga has been completely fermented to organic acids and is therefore no longer demonstrable in the faeces this is consistent w th the observations of Prader and co-workers [2] As starch is fermented much more slowly by the intestinal flora than the disaccharides starch can nearly always be demonstrated in the faeces in the case of insufficient starch digestion while only relatively little lactic acid is formed. This is the reason why in cystic fibrosis of the pancreas, in which only diastase is lacking, the diarrhoea is much less fermenting than in the case of invertase lactase or maltase deficiency

Enzyme Deficiencies

Deficiencies in sugar-splitting enzymes may be primary or secondary

1 *Primary deficiencies*

The primary congenital deficiencies are often familial, but may also occur solitary A lactase deficiency was seen in a father and son, whilst the grandfather s past history strongly suggested the same deficiency

In another family a lactase deficiency could be observed in two brothers and in again another family we d[illegible] an invertase deficiency in [illegible] regards the lactase defic[illegible] agreement with the find[illegible] co-workers [1], and th[illegible] the invertase defic[illegible]

phasized by the investigations of Prader and coworkers [2].

The severity of the disease is very different because the enzyme deficiency is more marked in one patient than in another. The greater the enzyme deficiency, the smaller the tolerance for the sugar involved and the more easily a fermentative diarrhoea develops.

The most striking feature in the past history of patients suffering from a congenital enzyme deficiency is that, when in the course of the first year of life starch or the involved sugar is added to the diet the child develops a diarrhoea that persists until the harmful carbohydrate is withdrawn from the diet.

A lactase deficiency becomes manifest very soon after birth, especially if the child is breast fed, in view of the high lactose content of the mother's milk. One must even ask oneself whether in many of the infants who do not thrive on mother's milk and in whom the cause is sought for in an abnormal composition of the mother's milk, this cause should not be found in a partial lactase deficiency of the infantile intestine.

Invertase and maltase deficiencies do not appear until saccharose/dextrine/starch is added to the diet, while a diastase deficiency only becomes manifest if the diet contains starch.

We believe that the prognosis of the primary enzyme deficiency depends on whether there is a relative or an absolute deficiency. In total absence of the enzyme it is not to be expected that recovery is possible; in the case of a relative deficiency complete recovery is not excluded in the long run, as we could already observe in several cases.

2. *Secondary deficiencies*

Besides the congenital primary enzyme deficiencies we should in practice also take account of deficiencies of a secondary nature.

If we realize that the sugar-splitting enzymes are mainly formed in the cell of the intestinal wall and develop their activity mainly in these cells, it is conceivable that *each process by which the cells of the intestinal wall are damaged either anatomically or functionally may cause a decrease of the enzymatic function*. If the affection is mild, the enzyme capacity will still be sufficient for a normal loading with carbohydrates, in view of the great reserve capacity of the intestine. As soon as the affection has become more extensive, however, the enzyme deficiency caused by it becomes manifest as soon as carbohydrates have to be digested, giving rise to diarrhoea. The diarrhoea, however, disappears if the *basal* intestinal affection that caused the enzyme deficiency has recovered.

This secondary enzyme deficiency may occur in children in whom, following an enteral infection, a diffuse enteritis persists. Unless this enteritis is accompanied by a considerable mucus production, the sugars reach the cells of the intestinal wall, but there is no splitting because of the enzyme deficiency; absorption remains therefore absent and the disaccharides fall victim to the bacterial flora. The absorption of monosaccharides, however, remains unimpaired.

If the enteritis is attended by a great mucus production, the sugars do not reach the cell of the intestinal wall. The absorption of all sugars, i.e. also of glucose, is therefore mechanically impeded in

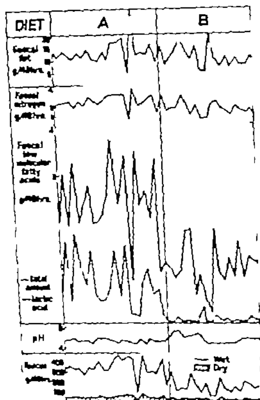


Fig. 1. Faeces examination in patient after partial jejunal and total ileectomy on a diet containing 25 g casein half hydrolysed, 25 g maize oil, 75 g glucose 75 g vegetables, 5 g yeast powder 250 ml raw apple juice, 600 ml water 60 g bananas, 30 g orange juice vitamins (B₁ included), pancreatin, in period A 30 g whey powder containing 70 lactose, and in period B 30 g whey powder containing 85 % lactose

this case. This may also cause a fermentative diarrhoea.

If the enteritis has been treated with good results also the enzyme function becomes normal again, as appears from the disappearance of the fermentation and as can be shown by means of disaccharide tolerance curves. After recovery of the disturbed absorption—irrespective of the fact whether this was caused mechanically (mucus) or was of a functional nature (enzyme deficiency)—no lactic acid will be produced any more so that this acid is no longer demonstrable in the faeces.

It is a known fact that dystrophic children may suffer from all sorts of enzyme deficiencies. It is therefore to be expected that in this case sugar-splitting enzymes will also be produced in an insufficient degree.

A diffuse enteritis and a marked dystrophy however are not the only affections that may give rise to secondary deficiencies in sugar-splitting enzymes, for this is to be expected in each metabolic disturbance of the cells of the intestinal wall of no matter what nature. It is especially true for infants who do not yet have an optimal enzyme production.

Because in infants and toddlers the loading of the intestine is relatively much greater than in adults, we should be on the alert for secondary enzyme deficiencies especially in these age groups.

A comparable situation is found in children and adults in whom the absorbing surface of the intestine has been reduced by intestinal resection, by which the enzyme capacity of the intestine has been decreased proportionately which means that the tolerance for foodstuffs has been lowered.

This case was encountered in a small boy 1½ years old, in whom about two-thirds of the small intestine had been resected. He had thus become very sensitive to overloading with food. As regards the sugars even a slight overloading gave rise to the appearance of lactic acid in the stools. Based on the amount of lactic acid excreted it was possible to determine exactly how much sugar and starch he

was able to tolerate maximally This is shown in Fig 1

Therapy

The therapeutic consequences of primary carbohydrate-splitting enzyme deficiencies are withholding of the sugars that cannot be split or addition of the missing enzymes [3] In the secondary deficiencies the basic disease should first be attacked, e.g., the enteritis or the dystrophy At the same time attention must be given to the sugar or starch intolerance by initially giving glucose as the sole carbohydrate If no attention is paid to sugar intolerance recovery will need a considerably longer time or even remain absent, as the vicious circle with which we are dealing in all these affections in the long run is not adequately broken through.

Summary

In addition to primary deficiencies in carbohydrate-splitting enzymes as cause of chronic fermentation diarrhoea attention should be given to transient secondary enzyme deficiencies e g., as a result of enteritis or dystrophy causing also fermentative diarrhoea

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Central Instituut for Nutrition
and Food Research T.N O
Catharijnesingel 61
Utrecht
The Netherlands

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From the Department of Physiology (Head: Professor Kaarlo Hartiala, M.D.) and from the Pediatric Clinic (Head: Professor Toivo Salmi, M.D.), University of Turku, Turku, Finland

The Ponderal Growth of Human Organs in Early Fetal Life

I Glandular Organs

by HEIKKI A SALMI MARTTI PULKKINEN and PETTER SAVOLA

Introduction

In recent years there has been an increased interest in the prenatal phase of child development, especially in the organogenetic period. The observations by Gregg are generally known. His observations stress the importance of early pregnancy regarding the health and the development of the fetus and the future child. In the last century and in the beginning of this one the macroscopic anatomist has assiduously described the dimensions of the human body. There are very accurate data on the development of the length, weight and size of the organs of a child. Due to various causes, primarily practical ones, our corresponding knowledge of the human prenatal period is rather scanty. The data in the literature are abundant but not comprehensive. A systematic and complete comparison of fetal organ weights with body development is essential. In earlier reports the fetuses have been described one by one [5 8]. Larger and statistically satisfactory materials are lacking.

The development of the thymus is of great interest. According to Wetzel [16], during the last seven months of the fetal development the thymus becomes enlarged from 1.. mg to 14 9 g in the ratio of 1 12 450 a rate of change much greater than that of the fetal body. According to Scammon [12], the weight of the thymus is more closely related to the weight than the length of the body. There is information on the weight of the pancreas after th first trimester [11]. Basic formulas have been derived for the growth rate of the external dimension of the fetus [2, 10, 14]. Kajava [4] has described the external dimensions of Finnish fetuses and compared them with Japanese data. The correlation, much needed in practice between the length of the body and the duration of pregnancy has been described and is presented in most hand and textbooks [1 9]. Most textbooks admit that the data available on the weights of organs are based upon very incomplete material [15].

In consideration of all this it is not strange that the facts on the growth of the weights of different organs during the prenatal period are not many nor homogenous.

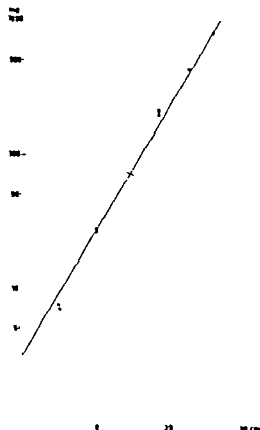


Fig. 1 The regression of the weight of the adrenal gland in regard to the crown–heel length of the fetus.

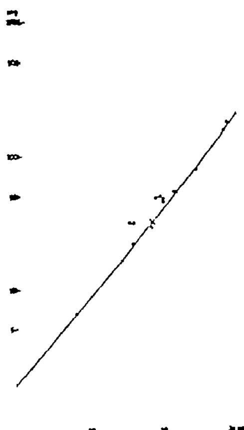


Fig. 2. The regression of the weight of the parotid gland in regard t the crown heel length of the fetus.

The authors have therefore considered the present study to be necessary to remedy this deficiency of information about such an important period of human development.

Material and Methods

The material consisted of 88 human fetu ses which were collected in connection with legal abortions in the years 1937 1960 The size of the fetuses varied from –5 cm to –8.5 cm crown–heel length, corresponding to the II–V months of pregnancy The material was considered to be normal, since the ind cations of the abortions did not arise from factors likely to be related to fetal or organ size When considering the paired organs, only the weight of one is given.

Method of preparation

Immediately after the operation the fet ses, surrounded by membrane were taken into a refrigerator (5 C) where measuring of the weight and the length of the fetuses took place The lifferent organs were also separated in the refrigerator The organs were weighed immediately with the Sartorius–Semimicro–Selecta balance ith an accuracy of ±0 000* g The possible drying of the smaller organs during the preparation was prevented by pipetting a drop of w ter onto the organ, which was kept on watch glass in the refrigerator The tissues and the

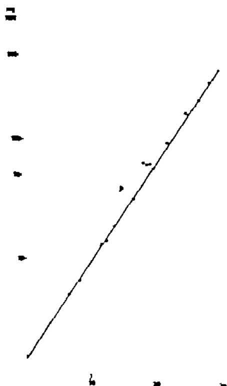


Fig. 3. The regression of the weight of the thyroid gland in regard t crown–heel length of the fetus.

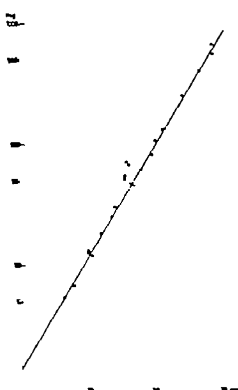


Fig. 4 The regression of the weight of the thymus in regard the crown–heel length of the fetu

TABLE 1 *The weight of human fetal glandula organs*

Organ	Number of fetuses	Length of fetus, cm		Mean weight of the organ, mg	Increase of the organ weight, log mg	
		Range	Mean			
Adrenal gland	44	2.5 – 28.5	14.3 ± 0.79	7 ± 13.6	0.095 ∓ 0.0183	0.903
Parotid gland	28	6.0 28.5	18 ± 1.05	23.9 ± 5.78	0.070 ∓ 0.0181	0.903
Thyroid gland	47	2.9 28.5	16.9 ± 0.79	32.4 ± 5.51	0.091 ∓ 0.009	0.954
Thymus	43	6.5 28.5	16.5 ± 0.82	46.7 ± 8.7	0.084 ∓ 0.0179	0.913
Pancreas	44	6.0 28.5	16.7 ± 0.83	52.7 ± 7.1	0.031 ∓ 0.023	0.881

number of determinations are hown in Table 1

Statistical methods

The regression of the logarithm f the length (x) f the fetus in relation to the weight (y) of the organ was calculated from the formula

$$y - \bar{y} \quad b_{yx}(x - \bar{x})$$

where the regression coefficient of y on x

$$b_{yx} = \frac{s_y}{}$$

in which and s_y re the standard deviations f and y and

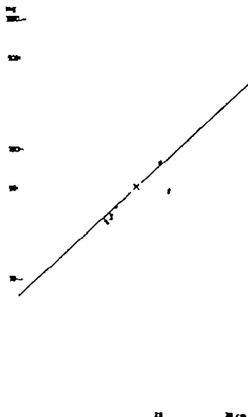


Fig. 5. The regression of the weight of the pancreas in regard to the crown–heel length of the fetus.

$$= \frac{s_y^2}{s_{xy}}$$

and in which, further

$$s_{xy} = \frac{1}{n-1} \sum_i \sum_j n_{ij} (x - \bar{x}) (y_j - \bar{y}).$$

The confidence limits of the regression coefficient β of the population at risk level p are

$$b_y \mp t_p \frac{s_y \sqrt{1 - r^2}}{s_x \sqrt{n - 2}}$$

while the number of degrees of freedom is n—. They are always calculated at risk level $p = 0.01$ (for example [3]).

Results

The results are given in Table 1 and Figs. 1–5

Discussion

The postnatal growth can be divided into growth phases during which the rate of growth is clearly greater than during the intervals [15]. During the intrauterine phase differences in the growth rates of weight and length can be observed. The rate of increase in weight is continually upward during fetal life while the rate of increase in length is maximal during the middle trimester. In the present study the weights of the organs taken from fetuses under 10 cm were generally located under the regression line. The organ weights of fetuses of 10–20 cm were above it while those over 20 cm were distributed about the line. One then gets the impression that until the fourth month there is a more rapid growth phase of the glandular tissues than between the fourth and sixth months. This was found in all the glands analyzed. Moss, Noback & Robertson [6] have observed that during this same period the growth of cranial bones slows down when the crown-rump length of 80–89 mm is reached. Our results are in agreement with these findings and also with those of *Olivier & Pineau* [7] who observed very clear turning points in the primate growth line when changing from the embryonic phase to the fetal phase. They observed two turning points of the human growth rate during the whole period of growth, a sharp change in the fetal phase and a more diffuse change during puberty.

It is not easy to separate the fetal pancreas from the surrounding collagenous

and fat tissue. Therefore it is best to be cautious in the interpretation of the measurement of this organ. The correlation coefficients between the weights of the organs and the lengths of the fetuses were > 0.9 which is very good. The corresponding value for the pancreas is only 0.681. The logarithmically calculated regression coefficients of the various organs were generally of the same order of magnitude.

Summary

The weights of the adrenal gland, parotid gland, thyroid gland, thymus and pancreas were analyzed in 64 human fetuses the length of which varied from 2.5 to 28.5 cm. The increase of the weight varied from log 0.031 to 0.095 mg/cm. There seems to be a more rapid growth phase of the glandular tissues until the fourth month, but it gets slower after this point.

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Pediatric Clinic
University of Turku
Turku
Finland

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From the Department of Physiology (Head Professor Kaarlo Hartiala, M.D.) and from the Pediatric Clinic (Head Professor Toivo Salmi, M.D.), University of Turku Turku, Finland

The Ponderal Growth of Human Organs in Early Fetal Life

II. Non-Glandular Organs

by MARTTI PULKKINEN HEIKKI A. SALMI and PETTER SAVOLA

There have been isolated studies of the growth of various fetal organs. Falk [1] determined the heart weights of fetuses of 8 and 9 months. Kowalski [ ] reported the kidney and liver weights of fetuses of the same age The comparative growth of different parts of the brain was studied by Noback & Moss [4]. However there has been no comprehensive approach to this important problem The authors previously reported the growth of glandular organs during the earlier pregnancy [5] The present study is concerned with the corresponding growth of non-glandular organs.

Material and Methods

The material consists of 7 human fetuses collected in connection with legal abortions. A more detailed description has been given in the previous work [5]. The organs examined and the number of them are given in Table 1 The preparative and mathematical methods have been given in the previous work [5].

Results

The results are given in Table 1 and in Figs. 1–8

Discussion

The growth of the organs analyzed here seemed to follow the same laws a

TABLE 1 *The weight of the human fetal non-glandular organs*

Organ	Number of fetuses	Length of fetus, cm Range	Length of fetus, cm Mean	Mean weight of the organ, mg	Increase of the weight, log mg cm	
Liver	69	[illegible]–[illegible]	12.6 ± 0.8[illegible]	1290 ± 274	0.09 ± 0.01[illegible]	0.923
Kidney	7	2.5–28.5	13.2 ± 0.74	100 ± 17.4	0.107 ± 0.011	[illegible]
Spleen	47	8.0–[illegible]	16.7 ± 0.77	32.4 ± 6.4	0.104 ± 0.0[illegible]	[illegible]
Stomach	59	[illegible]–8.5	14.7 ± 0.78	119 ± 18	0.083 ± 0.0132	[illegible]
Dig canal	19	[illegible]–11.0	8.0 ± 0.61	66.8 ± 18.6	0.109 ± 0.043	[illegible]
Heart	60	[illegible]–[illegible]	12.7 ± 0.85	197 ± 37	0.095 ± 0.0109	[illegible]
Lungs	65	[illegible]–28.5	12.0 ± 0.78	794 ± 170	0.107 ± 0.0[illegible]	[illegible]
Brain	62	2.5–28.5	13.2 ± 0.[illegible]	3390 ± 739	0.093 ± 0.157	

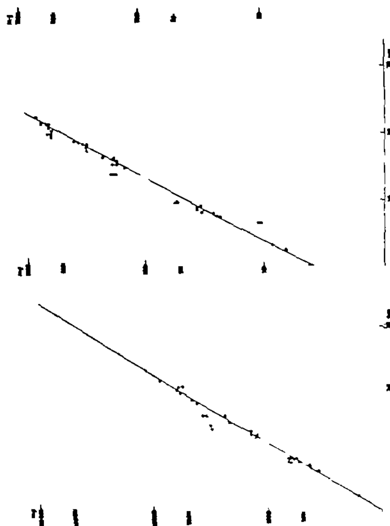


Fig. 1. The regression of the weight of the liver in regard to the crown-heel length of the fetus.

Fig. 2. The regression of the weight of the kidney in regard to the crown-heel length of the fetus.

Fig. 3. The regression of the weight of the spleen in regard to the crown-heel length of the fetus.

Fig. 4. The regression of the weight of the stomach in regard to the crown-heel length of the fetus.

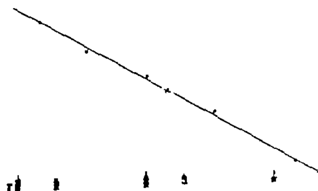


Fig. 5. The regression of the weight of the digestive canal in regard to the crown-heel length of the fetus.

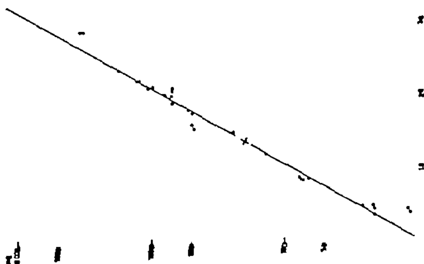


Fig. 6. The regression of the weight of the heart in regard to the crown-heel length of the fetus.

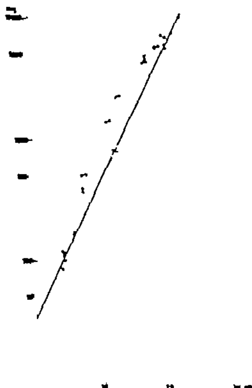


Fig. 7. The regression of the weight of the lungs in regard to the crown–heel length of the fetus.

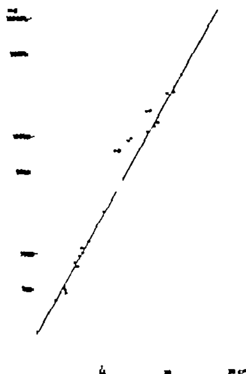


Fig. 8. The regression of the weight of the brain in regard to the crown–heel length of the fetus.

the organs presented in the previous work. In general the weights of tissues taken from fetuses under 10 cm were located beneath the regression line demonstrating a rapid phase of growth during the third and fourth months of fetal life. A definite retardation of growth was observed when passing to the fifth month of fetal life. Moss, Noback & Robertson [3] observed growth periods of same kind in bones. When comparing the regression of the length of the fetus and weight of the stomach or the weight of the digestive tract from fetuses under 11 cm, the growth in the latter case is threefold. This might of course, be due to differences between the growing rate of the different parts of the digestive canal. It would, however be more natural for this to reflect the period of very rapid growth already mentioned earlier relying on the fact that a whole digestive canal has been analyzed in fetuses of the average length of 7.0 cm, while the stomachs were taken from fetuses the average length of which was 14.3 cm.

Summary

The weights of liver, kidney, stomach, digestive canal, heart, lungs and brain were analyzed in fetuses, the length of which varied from 2.5 cm to 28.5 cm. The increase in the weight varied from kg 0.005 to log 0.199 mg/cm. It can be observed that in the organs examined the growth of the weight is retarded after the fourth month.

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Pediatric Clinic
University of Turku
Turku
Finland

permeability) per unit capillary surface area. There is little evidence that the porosity of the capillary endothelium is subject to physiological variation. For practical purposes, therefore, a change of CFC is more likely to be due to a change in capillary surface area.

Although actual filtration of fluid through the porous membranes of the capillaries is a transport mechanism of minor importance compared with diffusion, the study of filtration is, nevertheless, of considerable interest. First of all, as the capacity to filtrate is a function of the capillary surface area the CFC may be used as evidence of the local capillary vascularity of the particular tissue. Secondly, it is more or less likely that physiological influences relevant to filtration (such as changes of capillary surface area) also affect in a similar direction the quantitatively more important capillary transport mechanism of diffusion. It is further possible that the study of capillary filtration can indicate the occurrence of severe capillary damage. Another interesting possibility is to correlate the CFC of a tissue to the rate of local blood flow. In this way it may be possible to infer the relationship between "nutritional" and "non nutritional" blood flows. Lastly the study of capillary filtration is a field in which peripheral circulation, on the one hand, and the distribution and control of body fluids, on the other, meet. This is amply illustrated by the recent study of Mellander [19], in which he showed that the trans-capillary movement of fluid could be markedly influenced by activation of sympathetic vasoconstrictor fibres.

The present study is an attempt to determine in newborn infants the CFC in the lower limb. From the data on capillary filtration rates we will also try to answer the questions listed above as applied to newborn infants.

Methods

The rate of blood flow and capillary filtration in the lower limb of newborn infants has been measured under strictly standardized conditions by means of a water-filled plethysmograph. The construction of this and its use for measuring blood flow and for blood pressure determinations has been described in detail elsewhere [3, 4].

General principle

The lower limb of a newborn child was enclosed in a water filled plethysmograph connected to a sensitive volume recorder. The volume measured consists of the sum of solid tissues with intracellular fluid, and extracellular fluid, which in turn may be further divided into the extravascular tissue fluid and circulating blood. After a steady state has been established the limb does not change in volume but remains at an "isovolumetric state" [19, 1]. In this, the arterial inflow to the limb balances the venous outflow of blood, and, likewise, the net filtration on the arterial side of the capillary bed is equalled by a return of fluid on the venous side.

This equilibrium is now deliberately disturbed in a way which involves a positive stimulus to outward filtration. This is achieved by suddenly inflating a sphygmomanometer cuff on the thigh to a predetermined pressure. Obviously two types of volume changes is to be expected in response to this increase of venous outflow pressure. The first one is a gain of intravascular fluid, i.e. blood. This accumulation of blood will take place promptly and at a rate which equals that of arterial inflow. It will continue until the intravascular outflow pressure within the veins becomes higher than the effective

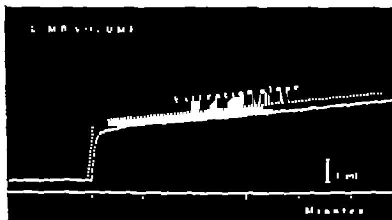


Fig. 1. Limb volume recording by the plethysmograph. Three separate phases are easily recognized: the "isovolumetric" state, the rapid rise when a cuff pressure of 40 mm Hg was applied (i.e. the ordinary plethysmogram) and the slow, long lasting and very constant gain in limb volume (the "filtration slope") from which the rate of outward capillary filtration can be calculated.

occluding pressure of the sphygmomanometer cuff after which blood will freely drain. As long as the cuff pressure is kept lower than the diastolic blood pressure the absolut rat of blood flow through the limb is little affected (see also Conrad & Green [7]), once the new steady stat has been established. Behind this initial and rapid change of limb volume is a passive elastic recoil of the capacitance vessels" in response to a gradual increase of hydrostatic pressure

The second type of volume change is related to the disequilibrium of hydrostatic and osmotic forces within the capillary bed, in fa our of the former which follows as the increase of venous outflow pressure is transmitted backwards to the capillaries. Once this increase of "mean capillary hydrostatic pressure is established, net filtration of fluid will take place from the circulating blood out in the extravascular tissue space. Whether or not the filtrated fluid will remain in the tissue space or shift t the cells does not matter In either case all of it must have passed through the capillary walls. From what is known about capillary filtration in animal [19 21], it is t be expected that this outward filtration of fluid will be a rather slow process compared with the initial and rapid accumulation of blood. On the other hand, it will continue for a considerable period of time, until tissue hydrostatic pressure has increased enough to create a new equilibrium of forces across the capillary wall. W can therefore expect the initial and rapid gain of limb volume t be followed by a much slower but continuous increase of limb volume from which net shifts in fluid across the whole capillary membrane can be inferred.

In Fig. 1 these three phases of limb volume recording are easily separated. The first part of the tracing represents the isovolumetric state After pproximately 30 seconds the sphygmomanometer cuff around the thigh of the infant was momentarily inflated at a pressure of 40 mm Hg This was accompanied by a sudden and rather rapid increase of limb volume completed within some 15 seconds, due to an accumulation of blood mainly in the venous vessels. The rise of the volume curve rather steep on account of the slow speed of the kymograph. From thi rise the rat f blood flow through the extremity can be calculated. After this second

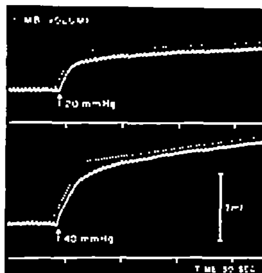


Fig 2. Typical "filtration slopes t cuff pressures *0 and 40 mm Hg from which the CFC was calculated Blood flow 5.2 ml/min/100 ml. CFC 0.010 ml/min/100 ml/mm Hg Not that pulse w ves and respiratory rhythm are reflected in the limb volume record.

phase the v lume curve show a distinct bend followed by a third phase during which limb volume contin ied to increase but now t a much slower speed. This lat gain of liml olume carried on for many min tes nd at a ery constant rat From thi "filtration slope the rat of outward filtration t a cuff pressure of 40 mm Hg can easily be leduced. As the volume of the tissues enclosed by the pletl ysmograph was known, the rat of l lood flow n th particula child could be calculated t mount to 3 4 ml min 100 ml. *Likewise the outward filtration of fluid* across the capillary membrane showed to be 0.30 ml min 100 ml at th particular cuff pressure f 40 mm Hg

Calculation of capillary f ltratio coefficient

So far the rat of outward f ltration has been correlated onl t the pressure reading on the blood pressure manometer To be able to calculat the CFC t necessary t correlat the rat of outw rd filtration to the disequilibrium of mean capillary hydrostatic pressure Obviously it will not be possible to determine mean capillary pressure d rectly Simply assuming that pressure of, e.g 40 mm Hg in the occluding blood pressure cuff is transmitted more or less quan titati ely backward to the capillary level is certainly difficult to j stify Firstly rest ing mean capillary pressure *prior* t the venous congestion l not known. Secondly the pressure energy lost by mechanical defor mation of the sphygmomanometer cuff and by compression of the tissues of the limb cannot be determined Thirdly the direct effect of the occluding blood pressure cuff is to raise enous outflow pressure How much of this increase of venous pressure is propagated into the capillaries depend on the relation between pre- and post-capillary resistances of the vascular region [19 1 2*]

W have attempted to circumvent these difficulties *in the following w y* The first two obstacles, that of the unknown resting capillary pressure nd loss of pressure energy from the cuff most probably do not change d ring the course of the tudy of an indi *vidual ch ild under the rather rigorou experi*mental conditions that we have adopted They could, therefore be eliminated by measuring the rat of outward filtration at *d ffere t* cuff pressures. F g illustrates how *thi could be achieved. In most infant only* two cuff pressures were pplied a rule *0 and 40 mm Hg The *d fference* in the rat of outward filtration at the tw separat period of enous congestion could then be worked out The approximation was ac cepted that the difference in *ffect* e in crease of venou outflow pressure at cuff pressures *0 and 40 mm Hg respect l approx mat ly also *0 mm Hg Experiment l evidence to justify th sumption will be reported on under the separat heading Relation between cuff pressure and enous pressure luring prolonged nous conge tion By this procedure we coul l correla a *d fference of f ltration rate to known d fference f venous outfl w pressure*

The third difficulty t estimat the

loss of pressure energy as the increase of venous outflow pressure was propagated in retrograde direction to the capillary level. As stated, this pressure loss is dependent on the relation between pre- and post-capillary resistance. This question cannot be subject to direct measurements in a study of this kind. However it is known from experimental work on this problem [19 20] that pre-capillary resistance at normal vascular tone comprises approximately four fifths of the total vascular resistance. This means that normally one-fifth of a pressure increase at the venous side will be lost before the capillary level is reached. In previous studies [2 4] blood flow blood pressures and thereby resistance t flow have been measured at standard conditions in the lower limb of the newborn infant. Children, who appear t be normal from a clinical point of view ha a peripheral resistance t flow comprising some 7 t 14 PRU (Peripheral Resistance Units). This is of the same order of magnitude as is known to pply for the same tissues in, .g., the cat. It therefore appears justified to assume that also in the new born hild by far the largest fraction of vascular resistance to flow is exercised by the pre-capillary blood vessels, mainly arterioles and pre-capillary smooth muscle sphincters. In this study we have made the general approximation that 80% of the total resistance is in the pre-capillary section. From this it follows that of an increase of venous pressure from 20 to 40 mm Hg between the tw periods of measuring only roughly 16 mm Hg will be transmitted backwards t the capillary section. In our calculation of the CFC we ha therefore divided the difference in rat of outward filtration t cuff pressures 20 and 40 mm Hg by the factor 16. As a matter of fact moderat differences in the relation between pre- and post-capillary resistance do not normally affect this calculation very much. A pre-capillary resistance of three-quarters t dilat tion of the blood vessels would gi factor of 15, whereas pre-capillary resistance of f ve-sixth t vasoconstriction ould give factor of 17 instead of the

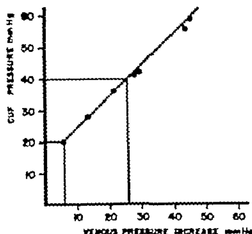


Fig. 3. The relation between cuff pressures and increases of venous outflow pressure during prolonged venous congestion in the adult forearm. Not that difference in cuff pressure of 20 mm Hg corresponds to an increase of venous outflow pressure of 20 mm Hg.

assumed 16 However as the ratio between pre- and post-capillary resistance tends t increase t vasoconstriction and to fall at vasodilatation the effect on our calculation of CFC is that at small flows the filtration coefficients calculated tend t err on the high side whereas t large blood flows the filtration coefficients tend to be too low Such a tendency should be kept in mind when our results are evaluated This "80% rule now appears to ha been almost generally adopted by various workers in this field [11 19 20, 21]. It is obviously unlikely that the relation between pre and post-capillary resistance will remain constant during major alterations of vascular tone known to occur in response to various neurogenic and metabolic influences. Nevertheless the approximation is well justified if only the effect on the calculation of CFC is kept in mind

Relation between cuff pressure and venous pressure during prolonged venous congestion

For obvious technical reasons decided to carry out this study on adult subjects.

Eleven people on the medical staff volunteered. By ordinary means a polythene catheter was introduced, percutaneously into the venous system of the forearm and connected to an electromanometer In most cases this was done *from one of the cubital veins* and in a retrograde direction if possible into one of the deeper muscular veins. As a rule, two or three sets of venous valves could easily be passed An ordinary sphygmomanometer cuff was applied on the upper part of the arm. The relation between the width of the cuff and circumference of the arm was pproximately the same as in our measurements on newborns. Cuff pressures were read on a mercury manometer There were *two questions we wished to have answers to Would the rise in venous outflow* pressure at a cert in cuff pressure remain constant during prolonged venous congestion? The answer was yes. When cuff pressures are plotted against simultaneous measurements of increases of venous outflow pressures, what are the relationships between them? These results were quite uniform and are illustrated by Fig 3. From this study we could therefore conclude that *a certain difference in cuff pressure (*0 to* 40 mm Hg) between the two periods of measuring capillary filtration rate correspond to approximately the same difference in venou outflow pressure

Standard experimental conditions

The child wa put in an Isolette incubator especially adopted as a "ellmat chamber for the newborn. A suitable plethysmograph and sphygmomanometer cuff was applied to the right limb [3].

The temperature of the incubator was 30°C and water temperature of the plethysmograph was kept at 34°C The upper part of the child was covered by it ordinary clothing We then waited for the child to fall asleep Not until the child had been asleep for at least 15 mm tes did we start our measurements. We first determined resting blood flow and the systolic blood pressure We deliberately avoided measuring diastolic blood pressure [4], since then *blood flow* had to be partially or completely interrupted during several short periods, a procedure which quit often disturbs the child. We then undertook our measurements on the rate of outward filtration at cuff pressures *20 and 40 mm Hg (sometimes 10 and 30 mm* Hg, or at more than two cuff pressures) In the present study we had an interval of 10 to 15 minutes between the two period of measuring. (We have now accepted to shift directly from *0 to 40 mm Hg, which seems to work just as well.) In order to be included in the present report *the child had to remain asleep duri g the whole period of measuring* Thi was concluded by once again measuring resting blood flow and systolic blood pressure *A vast number of trial had to be given up*

Material

Forty-six children were accepted in this study They were all f ll terms babes and at repeated examination they had all been considered as "normal Great care as taken to exclude children who showed the slightest symptom of disturbances in respiratory or cardiac function. Since the adaptation to extrauterine cond tions, as regard peripheral circulation of the extremities, may last for the first 12 hours, even t an uncomplicated delivery we also excluded those children which were less than 1 hours of age Otherwise they were all in their *first week of lif*

Lastly it should perhaps be pointed out that owing to the technical difficulties in study of this kind the figures reported should not be considered as exact values on the capacity of the vascular bed of a certain region to transfer fluid across capillary walls. They should rather be looked upon as attempt to estimate the pproximat magnitude of this function.

Results

The rate of blood flow in the foot and calf

In a previous report [3] the rat of *blood flow* at early and late neonatal age

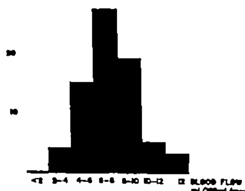


Fig. 4. The rate of blood flow at standard conditions in the lower limb of 73 "normal" full-term infants.

was found to vary roughly from 5 to 10 ml/min/100 ml in a group of 15 newborns. Fig 4 summarizes additional observations on 73 infants As might be expected a few infants showed smaller or larger flows than previously observed in normal children We doubt, however whether these children, who had flow rates considerably smaller than 5 ml/min/100 ml or larger than 10 should be considered as being in normal circulatory states. They did not remain at these extremes for any long period of time Otherwise the flow rates in this large group of newborns compare well with those previously reported.

The capillary filtration coefficient of the foot and calf

The 46 children in which measurements of the CFC could be completed in accordance with our "rules" are summarized in Fig 5 All but three lie within the limits 0 005 and 0.02 ml/min/100 ml/mm Hg

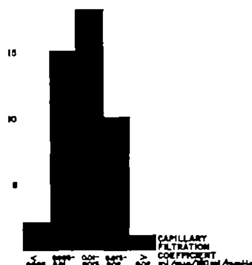


Fig 5 The CFC at standard conditions in the lower limb of 46 normal full-term infants.

Thirty five were within 0 0075 and 0 0175 whereas six had lower and five higher records on CFC. The mean value for the total number of newborns was 0 011 (±0 004) ml/min/100 ml/mm Hg

The relation between the rate of blood flow and capillary filtration coefficient

In Fig 6 the CFC of individual children has been plotted against the rate of blood flow It is obvious that this group of children is rather heterogeneous, both as regards the rate of blood flow and CFC. (Why they should differ so markedly is impossible to decide It seems natural to assume that they may also differ as regards their metabolic state It is also likely that two children having approximately the same rate of volume flow do

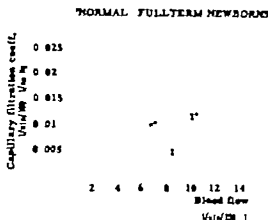


Fig. 6. The relation between the rate of blood flow and CFC in the lower limb of 46 "normal full term infants.

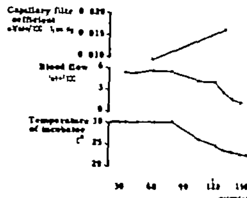


Fig 7 Changes of blood flow and CFC in new born child when exposed to lowered ambient temperature. Note the increase of CFC while blood flow was reduced.

not necessarily have identical metabolic states, as regards limb tissues.) Although the scattering of data is great it seems possible to draw one conclusion from Fig 6 There is obviously no direct relationship between the rate of blood flow and the CFC in such a way that CFC increases parallel to the rate of blood flow To us it seemed logical that at larger blood flow there would also be a greater number of capillaries open to circulation and consequently a higher CFC The relation between blood flow and CFC seen in Fig 6 may possibly be the opposite since children with small flow sometimes had very high CFC Although the scattering is great our measurements were made on a considerable number of infants, and we therefore made a statistical analysis. It was then found that the group of blood flow values lower than the median had a somewhat higher CFC than the group of flow values, which were above the median value for blood flow However this difference was not significant on the 5 level.

Changes in blood flow and capillary filtration coefficients to lowered ambient temperature

In a smaller group of children we were able to carry out measurements of blood flow and CFC at different levels of temperature in the incubator To do this we had to do measurements at standard conditions first Then we had to lower the temperature gradually after which all measurements were repeated During the whole of this period the child had to remain asleep. Needless to say our number of failures has been great In all cases the rate of blood flow decreased markedly and in most cases down to one-third or even less of initial blood flow In no case did we find any simultaneous reduction of CFC On the contrary CFC usually increased rather significantly This is illustrated by Fig In this child blood flow fell from 5.0 to 1 4 ml/min 100 ml. Meanwhile the CFC increased from 0.0 to 0 017 ml min 100 ml mm Hg

Discussion

In the present study an attempt was made to get information on capillary fil

rates of the vascular supply to a region in relation to the rate of ... mal blood flow. At first sight such ata would appear as perhaps interesting ... than of any real importance, when comes to evaluating the circulatory state the newborn.

... determining the rate ... capillary filtration

The flow through the porous membranes the capillaries per unit tissue is dependent on the viscosity of the fluid, the "hydraulic conductivity" (or "Wasserdurchlässigkeit") of unit membrane area, the capillary surface area and hydrostatic and osmotic pressure gradients across the membrane. Experimental evidence shows that the rate of filtration is related to the viscosity of the fluid, which is in turn dependent on the temperature of the preparation [21]. The effect of viscosity is comparatively small, and there is little reason to suggest that the viscosity of the ultrafiltrate of blood plasma will vary much under normal physiological conditions. On the other hand, these observations have been taken as evidence in favour of the view that capillary filtration of fluid takes place by viscous flow through pores in the capillary membrane [*1].

The studies by Pappenheimer and coworkers [1] have shown that the normal impermeability of capillary membranes to plasma proteins is retained in the rather crude hind leg preparation, and that changes of temperature over a range of 8 to 44°C did not produce any evidence of capillary damage in this respect. There is also good evidence that the functional integrity of the capillary endothelium is not altered by a reduced oxygen supply unless this becomes extreme [13]. "Hydraulic conductivity" of unit membrane area is therefore probably not subject to physiological variation, but may be assumed to remain constant in the type of study that we have performed, even if the individual child may vary in other respects as regards the circulatory state as, e.g. the rate of local blood flow.

The protein osmotic pressure is still another factor which has to be considered when the rate of capillary filtration is studied. There is however little reason to assume that the concentration of blood proteins will change much during the course of the study of an individual child. The escape of fluid from the circulating blood which takes place during our measurements is certainly far too small to affect significantly blood protein concentration. Experimental evidence on adult also indicate that during venous congestion very little protein is lost to the tissue fluid, so that tissue protein osmotic pressure is probably not affected [16].

In a study of this kind the rate of filtration across the capillary membrane will therefore depend primarily on two variables i.e. the capillary surface area available and the hydrostatic pressure gradient acting over the membrane. Per unit pressure change the rate of filtration will hence be a measure of the available capillary surface area or the number of capillaries open to circulation. From this point of view studies on capillary filtration rates have a considerable status since the number of capillaries per unit tissue besides the rate of blood flow through the tissue is the main limiting factor in the transport of materials between the circulating blood and the extracellular fluid spaces creating the im

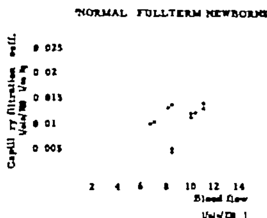


Fig 6. The relation between the rate of blood flow and CFC in the lower limb of 46 "normal" full term infants.

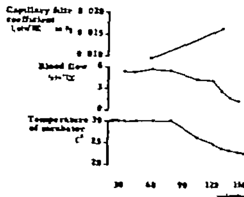


Fig 7 Changes of blood flow and CFC in new born child when exposed to lowered ambient temperature Note the increase of CFC while blood flow was reduced.

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Changes in blood flow and capillary filtration coefficients to lowered ambient temperature

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Discussion

In the present study an attempt was made to get information on capillary fil-

changes due to vascular tone. This of the pressure plethysmograph is probably partly reduced by the fact that it necessitates repeated interruption of the circulation and thereby easily disturbs any steady state in circulation. With this method the change in the rate filtration accompanying unit rise (1 cm of water) in venous pressure amounted to 0.0033 ml per minute per 100 ml of forearm, when the congestion periods were 10 minutes long [17]. Assuming that 80 % of the rise in venous outflow pressure is propagated to the capillaries the capillary filtration coefficient of the human adult forearm would be 0.0055 ml/min/100 ml/mm Hg. Values of approximately the same order have been reported more recently by Kitchin [1*]. These values are considerably lower than ours on the foot and calf of the newborn infant. This difference may partly be due to technical circumstances, such as a lower temperature in the plethysmograph and also a lower environmental temperature applied in these studies on adults. One would, a priori expect that a lower temperature would reduce the number of capillaries open to circulation and hence filtration rates. However as has been described in this paper lowered temperature although it reduces volume flow markedly had no such effect on the filtration rate. As a matter of fact in several infants the capillary filtration rate increased parallel to this decrease of flow (see Fig 7). There is thus little evidence to suggest that the lower temperature conditions in the study by Landis & Gibbon [17] effected a functional closure of nutritive capillaries. The difference in filtration rates between adults and newborns rather seems to be an expression of a smaller capillary surface per unit volume of tissue in the human adult forearm compared with the foot and calf of the newborn. Further support for this interpretation of our data is suggested by the higher rate of resting blood flow in infants [3] than in the extremities of the adult [*]. Of probably greater importance is our recent observations that the maximal blood flow capacity in the lower limb of newborn babies (full term and premature) measured as reactive hyperaemia in response to a 10-minute period of arterial occlusion at 40°C (Celander & Mårild [5]) seems rather to be higher than in the extremities of the adults.

The combined evidence based on determinations of resting blood flow maximal blood flow capacity and capillary filtration coefficients would therefore suggest that the vascularity of extremities (the number of capillaries per unit volume of tissue) is higher in the newborn than in the adult

Regional circulation of the newborn as compared with adults

Krogh [14] has stressed that different tissues in different species may show a widely varying degree of vascularity. In general, there seems to be a fair correlation between the number of capillaries per unit tissue and oxygen consumption, i e the rate of metabolism. Dawes and coworkers [8] have shown that in the lamb there is a marked increase of oxygen consumption after birth. This does not necessarily mean that the basal metabolic rate prior to birth is abnormally low. The steep rise when extrauterine life commences is probably well explained on the basis of added metabolic demands caused by the lower am

bient temperature increase of muscular activity in maintaining respiration body posture and tone suckling digestive processes, kidney and liver function, specific dynamic action of food, etc [8]. Another factor of probable importance in this connection is the long-debated question of a hypoxic state during intrauterine life. That a true hypoxic state exists is beyond doubt. It should perhaps be stressed that *measurements of* oxygen saturation and oxygen tension in various systemic arteries have a limited value when it comes to evaluating the oxygen supply to the foetus. Similar data obtained from the venous side of the systemic circulation have a considerably greater informative value since this blood reflects the metabolic state in this respect at the capillary level. Although such data are meager [*6] they clearly indicate that to adult standards the foetus is in a true hypoxic state. It has often been postulated that hypoxia is a stimulus promoting development of a larger number of capillaries (for ref see e.g. the review by Korner [13]) Actual proof for such an assumption has been difficult to obtain. Nevertheless, such a mechanism seems plausible especially during the period of rapid growth at late pregnancy. It is a well-known fact that the metabolic rate of the newborn infant per unit weight is about twice that of the adult [25]. Even if the lower limb of the newborn contains more skin and less skeletal muscle than that of the adult the rate of metabolism in the limb is, if anything, higher in the newborn than in the same part of the adult. *The higher rate of blood flow and the larger capillary surface area per unit tissue volume during resting conditions should most probably be looked upon as a physiological adaptation in the newborn infant to the higher demands of metabolism.*

The vascularity of the newborn

It is known that most tissues have a local "blood flow reserve" created by the basal vascular tone which is essentially of local origin (for further information, see e.g. Folkow [10]). The question then arises, is this larger flow and greater capillary exchange area mainly of functional origin and due to the fact that part of this local blood flow reserve is utilized by the newborn in response to his higher metabolic needs? Or is there an anatomical background so that the newborn is supplied with a greater number of capillaries per unit weight of tissue? To us the latter alternative seems the more plausible one since the maximal blood flow capacity of the tissue seems rather to be higher in the newborn than in the adult.

Quantitative data on the anatomy of the peripheral blood vessels in the newborn are meager and are restricted to injection preparation after death [9], or to in vivo microphotographs from superficial regions such as the skin [*4] or conjunctivae [1]. In general, the conclusions based on these studies have been that, compared with the adult the newborn is poorly supplied with finer vascular structures, to which the "exchange function" of the circulatory system must be attributed. So e.g. Arajärvi [1] states that "the very thin, equivalent to adult, capillaries were few or non-existent". From a functional point of view we could not agree less. Quantitative data on resting blood flow and peripheral resistance to flow on the capillary filtration rate indicating the capillary surface area and on the very

igh "local circulatory reserve" [5] all nfirm the concept of a very rich vascular upply and a high capillary exchange capacity in the skeletal muscle and skin f the newborn. There is an interesting lk between resting rate of blood ow capillary filtration coefficient and oxygen consumption per unit weight of Roughly they all seem to be about wice as large in the newborn as in the dult.

Permeability"

Virtually nothing is known about per eability of the capillaries of the newborn from those of the kidney and the transfer of plasma proteins and other materials across the blood–C.S.F barrier (for references see the review by Zetterström [28]) The greater capillary fragility of the newborn in response to negative pressures, as shown long ago by Ylppö [28], should not be considered as measurements of capillary permeability in a physiological sense The assumption [*6] that a greater capillary fragility also suggests greater capillary permeability is therefore difficult to justify In respect of the transfer of water across the capillary walls, the higher filtration coefficients that we have obtained in newborn could f course indicate a greater permeability (or hydraulic conductivity) *per unit* capillary surface area or a greater capillary surface area per unit tissue volume W ha dvocated the latter explanation mainly because other data on resting blood flow maximal blood flow capacity and oxygen consumption harmonize well with such a concept The passage of w ter and other lipid insoluble molecules is limited to area between the endothelial cells and the total cross-sectional area of these aqueous channels comprises less than 0.2 % of total capillary surface area Lipid-soluble molecules, such as oxygen and carbon dioxide in addition pass the cell membranes and at rates many times greater than, e.g that of water [21 22] The newborn child would therefore have little benefit in meeting its metaboli needs by an isolated increase of the inter cellular areas, but little or none of the endothelial cells Such a fundamental dif ference in structure of capillaries in the newborn *versus* the adult seems very unlikely

Capillary filtration in relation to regional blood flow

A few words should be said on the rela tion between the rate of local blood flow on the one hand, and capillary surface area available for exchange purposes, on the other One would *a priori* assume that any change in flow rate would be accom panied by a similar change in the number of capillaries open to circulation and hence capillary filtration. However this is not necessarily so The resistance to flow and thereby volume flow is determined pri marily by the degree of constriction in the arterioles. The number of capillaries open to circulation and thereby the distribution of the volume flow is determined primarily by the smooth muscle pre-capillary sphinc ters Arterioles and pre-capillary sphinc ters are both subject to nervous control [10 11] They are lso constantly influenced by the local chemical environment n su h way that the restricting influences of the vasoconstrictor nerves are balanced by the d lator ction of a large number of metabolites mainly of local

origin. Any important neurogenic reduction of volume flow may therefore be restricted and counteracted by this dilator influence on smooth muscle tone of the arterioles. It may even be partly compensated for if the dilator influence is more pronounced on the pre-capillary sphincters than on the arterioles. In this case more capillaries would open up and the reduced volume flow would now be distributed over a larger exchange surface in the capillary network. Thereby the distances which molecules have to diffuse from the circulating blood to the metabolically active cells and vice versa is reduced and so is the velocity of circulation in an individual capillary *A greater capillary surface area shorter distances to the cells and a longer period of time available for equilibrium between blood and tissue fluid should then constitute important compensatory mechanisms by which reductions of local blood flow are met with in order to maintain the most vital exchange function of the circulatory system* in spite of e g reductions of cardiac output or when the blood flow in general hæmodynamic stress situations has to be deviated to the most important tissues such as heart and central nervous system. This is how we would like to interpret our otherwise rather paradoxical findings that the children who had the smallest volume flows seemed to have if anything, not a reduced but a larger capillary filtration capacity even than those who had a larger blood flow Similarly in response to a lower ambient temperature the individual child showed a reduction of blood flow down to one-third or even less (probably mainly due to closure of A–V shunts in skin circulation) In spite of that the capillary surface area available generally increased to judge from the increase of CFC. Little is known about such an "escape phenomenon in response to reductions of volume flow Mellander [10] and Folkow & Mellander [11] found in their preparation of the hind part of the cat that, when blood flow was reduced by stimulation of vasoconstrictor nerves, the immediate effect on the capillary filtration rate was a decrease This was just opposite to our present findings in the newborn. However later (although yet unpublished) experiments by this group [6] have conclusively shown that upon prolonged sympathetic nerve stimulation there is this "escape phenomenon also in the cat, so that already after some minutes the rate of capillary filtration gradually increases to levels which may be considerably higher than those prior to stimulation It seems likely that this highly interesting adaptation of the regional blood flow in relation to available volume flow of blood will attract future interest in experimental work on peripheral circulation.

Summary

1 By applying the venous occlusion plethysmograph the rate of blood flow and the rate of capillary filtration has been measured in the foot and calf of the newborn infant during normal sleep

2 The rate of blood flow in 73 full term infants was essentially the same as that previously reported

3 The capillary filtration coefficient (CFC) in 46 normal full term infants was 0 011 ($\pm$0 004) ml/min/100 ml/mm Hg *The CFC is considered as a measure on the available capillary surface area.* Compared

adults, newborns have approximately as large a CFC and the conclusion made that per unit volume of tissue the newborn seems to have a correspondingly [illegible] capillary surface area. Why this be so is discussed.

4. Children with smaller volume flows possibly higher CFC and, therefore probably a larger available capillary surface area per volume of tissue. In response a lowered ambient temperature volume blood flow was reduced, whereas the CFC increased. This important shift in the distribution of local volume flow is considered as an "escape phenomenon" by which the local capacity of transporting molecules across the capillary membrane is maintained in spite of reductions of local blood flow.

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Barnsjukhuset
Göteborg
Sweden

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rom the Department of Virology University of Helsinki, and the Folkhälsan Children's Institution, H lsinki, Finland

Clinical and Immunological Studies on a Live Attenuated Measles Virus Vaccine in Infants and Children[1]

by P HALONEN P FORSSELL, H. HALONEN O PETTAY R. STENSTRÖM, S. ÖHMAN and N OKER BLOM

The immunological efficacy and the absence of communicability of live attenu ated measles virus vaccine has been described by Katz & Enders [8] and others [1 2, 4 7 9–11 13–18 1 24]. Since im munity to natural measles infection shortly after vaccination has also been reported [6 7 14 15] the final acceptance of the vaccine for routine pediatric immunization will presumably depend on the per sistence of the immunity conferred and on the severity of reaction to vaccination.

According to earlier studies, fever and rash may result from the vaccination. It is generally concluded, however that the reactions are mild and that the well being" of the children with reactions is apparent [10] On th other hand, vaccination may occasionally be accompanied by high fever and malaise [18]. It has also been shown that marked reduction in such reactions can be obtained with small doses of gamma-globulin without suppression of the antibody response [17 18].

The present study has been undertaken mainly to gain further information regarding the reactions caused by subcutaneously inoculated attenuated measles virus vaccine prepared from the chick embryo passaged Edmonston strain in institutionalized children and th effect of gamma-globulin on such reactions. In addition, the serological response to vaccination was tested by complement fixation (CF) and hemagglutination inhibition (HI) techniques.

Material and M thods

Design and operation f study The clinical material consisted of 38 healthy children in a children institution in Helsinki. This institution is also a training institut for nurses. The children were divided into two groups, A and B Although the children in the two groups were mixed in eight rooms, in the highly hygienic conditions of the institution little direct contact was possible between the younger children t any time and none between the older ones during febrile periods. Isolation measures such as are adopted in hospitals for infectious diseases were not, however taken.

Group A was vaccinated on June 15, 1961 The blood specimens for serological studies were taken before and 4 weeks and 10 weeks after vaccination. The blood specimens for clinical studies were taken before and 13–15 days after the vaccination. EEG tracings

[1] A preliminary report of some of the results presented in this paper was given at the International Conference on Measles Immunization in Bethesda, November 7–9 1961.

were made from 10 children both before and about 14 days after vaccination. A chest X ray examination of each child was done before and 16–18 days after vaccination.

Clinical observations on the children were made daily by two experienced pediatricians from the hospital for infectious diseases.

Group B which served as a control in the first part of the study was then vaccinated on July 6, 1961 Each child in this group received gamma globulin, 0 03 ml/kg of body weight on the fifth day after vaccination. The blood specimens for serological studies were taken before group A was vaccinated 6 weeks later and 4 weeks after the vaccination of group B The blood specimens for clinical studies were taken and the clinical observations were made as in group A, except that no X ray examinations or EEG tracings were included.

Vaccine. The live attenuated measles virus vaccine was obtained from Lederle Laboratories, American Cyanamid Company New York, N Y ("Modified Live Measles Virus Vaccine") It was prepared from the 19th chick embryo passage of the Edmonston strain. The infectivity titer of the vaccine was 3 0 $TCID_{50}$ per ml when titrated in human amnion cells of a continuous line [5] The lyophilized vaccine was reconstituted immediately before use with 2 ml of distilled water and 0 5 ml of this reconstituted vaccine was injected subcutaneously into each child

Gamma-globulin Gamma-globulin was obtained from the Finnish Red Cross Blood Transfusion Service The measles neutralization antibody titer of the lot was 1 160, when 100 $TCID_{50}$ of the virus was employed.

Serological procedures The preparation of CF antigens and the CF techniques used have been reported elsewhere [5] The hemagglutination inhibition technique is based on that described by Rosen [19] The hemagglutinating antigen was prepared by ultracentrifugation of measles virus grown in tissue culture at 20 000 r.p.m. in a Model L Spinco (head no. 21) The pellet with one-tenth of the supernatant was collected and this antigen was stored at −25°C The hemagglutination titers of the various antigen lots were 1 16 to 1 64 In the hemagglutination inhibition test the antigen dilution containing four hemagglutinating units and the serum dilutions were incubated overnight at +4°C before the addition of rhesus erythrocytes

Results

Clinical reactions after vaccination

Vaccination without subsequent gamma globulin administration All the 22 children of this group reacted with fever ranging from 38 0 to 41 4°C (rectal) (Tables 1 and 3) With a few exceptions the onset of fever occurred on the seventh to ninth day after vaccination. The mean duration of fever was 3.5 days.

A rash appeared in all but three of the children. In eight children it was of a generalized maculopapular type and hardly distinguishable from a natural measles rash of moderate degree. The onset of rash was between the ninth and twelfth days after vaccination and the mean duration was 4 days Koplik spots were seen in eight children, and nine had a mild cough A decreased white cell count was observed in many children, but the blood specimens for clinical studies were taken a few days too late to allow calculation of the true incidence of leukopenia. The chest X ray finding was normal in all 22 children. Normal EEGs were also obtained in each of 10 children examined. No otitis media or other complications occurred. The clinical features in one child representative of the group are shown in Fig 1

None of the children in the unvaccinated control group had symptoms which could be attributed to an infection with the attenuated measles virus.

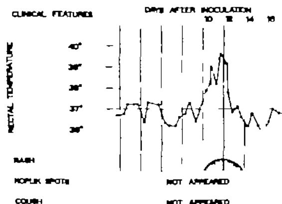


Fig. 1 Representative clinical features of a child after inoculation of live attenuated measles virus vaccine without subsequent gamma-globulin administration.

Two to three days after vaccination many mild cases of colds with nasal discharge but without a cough appeared in the institution in both vaccinated and unvaccinated children. In the latter group two children had low fever of 38°C or less. This concomitant infection may explain the early fever in two of the vaccinated children.

Vaccination with subsequent gamma-globulin adm nistration. Of the 16 children receiving gamma-globulin on the fifth day after vaccination, 1 reacted with fever ranging from 38 1 to 40 5°C (Tables 2 and 3) The mean duration of fever was 3 days A mild rash of roseola infantum type ppeared in six children. No Koplik spots were seen and no complications occurred

Serological response to vaccination

The CF antibody and HI titers before and after vaccination are shown in T bles 1 and Of the children in the first group (group A) who did not receive gamma-globulin, none had CF or antihemaggl tinating antibodies before vaccination nd each developed antibodies after vaccina tion. Of the children in group B who received gamma-globulin, two (nos 26 and 28) had antibodies in prevaccination specimens. These two did not respond to vaccination (Table 4) whereas all the others developed CF and antihemagglu tinating antibodies. The geometric mean CF antibody and HI titers were slightly lower in group B receiving gamma-globu lin than in group A, which did not receive it (Table 3)

Discussi n

In accordance with earlier studies, a good serological response to subcutane ously inoculated ttenuated measles virus vaccine was obtained in children without measles antibodies. A small dose of gamma-globulin given 5 days after vaccination did not significantly depress the serological response

The complete absence of complications in these measles-vaccinated hildren is also in conformity with the earlier reports In this connection it may be interesting to not that during the last measles epidem

TABLE 1 *Clinical and serological responses of infants and children to attenuated measles virus vaccine without subsequent gamma-globulin administration*

Child no.	Age		Fever			Rash					CF antibody titer		HI titer	
	Years	Months	Day of onset	Duration	Max. temp.	Day of onset	Duration	Extent	Koplik spots	Cough	Before vaccination	After vaccination	Before vaccination	After vaccination
1	1	4	4	8	41.4	—	—	−	−	+ +	0[a]	64	0[b]	[illegible]
3	1	4	9	4	39.3	10	5	+ +	−	−	0	128	0	[illegible]
5	1	11	9	3	38.7	10	3	+	−	−	0	128	0	[illegible]
7	1	2	9	3	39.1	9	6	+ +	−	+	0	64	0	[illegible]
11	1	7	8	3	39.1	10	3	+ +	+	−	0	512	0	[illegible]
15	1		9	1	39.3	10	5	+ + +	−	−	0	64	0	[illegible]
17	1	11	8	3	40.1	10	3	+ +	−	+ +	0	16	0	[illegible]
19	0	8	8	3	38.0	10	3	+	−	+ +	0	32	0	[illegible]
1	2	3	7	4	38.5	—	—	−	−	−	0	16	0	[illegible]
23	2	1	5	7	40.5	11	3	+ +	+	−	0	32	0	[illegible]
[illegible]	1	5	8	3	40.4	10	5	+ + +	−	−	0	32	0	[illegible]
27		0	7	4	39.4	10	3	+	−	−	0	512	0	[illegible]
29		2	7	5	40.7	11	4	+	+	−	0	1024	0	[illegible]
31	2	8	6	4	40.1	11	4	+	−	−	0	32	0	[illegible]
33	1	4	8	4	39.1	11	4	+	+	+ +	0	64	0	[illegible]
37	1	5	7	4	40.2	11	4	+	−	+ +	0	512	0	[illegible]
39	4	6	8	3	40.3	10	5	+ +	+	−	0	128	0	[illegible]
41	1	11	9	3	40.1	11	4	+	−	+	0	128	0	[illegible]
43	1	3	10	2	38.5	12	3	+	+	+	0	64	0	[illegible]
45	1	4	6	4	39.3	11	4	+	+	+	0	128	0	[illegible]
47		8	8	3	39.6	12	3	+	+	−	0	64	0	[illegible]
49	1	2	8	3	38.9	—	—	−	−	−	0	64	0	[illegible]
	1	10	7.5	3.5	39.6	10.5	4					90		[illegible]

a 0 = < 4.
b 0 = < 10.

io in Helsinki in 1960 for instance, the complication rate (otitis media pneumonia, encephalitis) in measles patients hospitalized for medical and social reasons was about 30 % [5]. Furthermore Kohn & Koiransky [12] have reported that only 90 % of measles patients have a normal chest X ray finding and this has been confirmed in the Hospital for Infectious Diseases in Helsinki [22 23]. In the present study however the chest X ray findings were normal in each of 22 vaccinated children. Similarly Gibbs *et al.* [3] have reported abnormal EEG s in about 50 % of measles patients, while in the present study it was normal in each of 10 children tested.

The clinical reactions after vaccination also resembled those reported in earlier studies The clinical symptoms as a whole were more intense however than had been expected. In several of the vaccinated children the fever and rash were indistinguishable from those of moderate natural measles infection. Moreover a cough developed in several children, although it was clearly less severe than in natural measles patients. The concomitant cold infection in the institution may have aggravated the reactions. On the other

TABLE 5. *Clinical and serological responses of infants and children to attenuated measles virus vaccine with subsequent gamma-globul n administration*

Age		Fever			Rash			Koplik spots	Cough	CF antibody titer		HI titer	
	Months	Day of onset	Duration	Max. temp.	Day of onset	Duration	Extent			Before vaccination	After vaccination	Before vaccination	After vaccination
0	[illegible]	[illegible]	2	38.4	—	—	−	−	−	0^a	128	0^b	160
1	2	8	4	39.7	—	—	−	−	+	0	256	0	160
0	[illegible]	[illegible]	3	38.1	[illegible]	2	+	−	−	0	32	0	160
0	[illegible]	[illegible]	3	40.2	10	5	+ +	−	−	0	[illegible]	[illegible]	80
0	[illegible]	—	—	—	—	—	−	−	−	0	64	0	80
0	[illegible]	[illegible]	1	38.1	—	—	−	−	−	0	16	0	80
0	[illegible]	—	—	—	—	—	−	−	−	[illegible]	0	20	0
0	[illegible]	—	—	—	—	—	−	−	−	[illegible]	4	80	20
0	10	[illegible]	2	38.5	10	3	+	−	−	0	64	0	160
0	[illegible]	[illegible]	1	38.7	[illegible]	4	+	−	−	0	32	0	160
0	10	[illegible]	5	38.8	—	—	−	−	−	0	64	0	160
0	[illegible]	—	—	—	—	—	−	−	−	0	64	0	160
1	3	7	3	38.5	[illegible]	1	+	−	−	0	64	0	160
0	7	[illegible]	2	38.7	—	—	−	−	−	0	64	0	160
[illegible]	[illegible]	[illegible]	2	39.7	—	—	−	−	−	0	64	0	160
2	2	7	[illegible]	40.5	10	1	+ +	−	−	0	128	0	160
1	0	7.8	3	38.9	9.6	2.8					40		80

a 0 = < 4.
b 0 < 10.

TABLE 6. *Summary of the cl nical and serological responses of children without pre-vaccination measles antibodies to attenuated measles virus vaccine with or without subsequent gamma-globulin administration.*

Group	No. of children without prevaccination antibodies	Fever	Rash	Koplik spots	Cough	Mean post vaccination titer CF	HI
Group A (no gamma-globulin)	22	22 (100%)	19 (ca. 85%)	8 (ca. 35%)	9 (ca. 40%)	80	240
Group B (gamma-globulin 0.03 ml/kg)	14	1 (ca. 78%)	8 (ca. 40%)	0	1 (ca. 8%)	80	140

hand, it is probably difficult to select a time period for vaccination when a group of children of this age are without some minor illness [20].

In the vaccinated children who received gamma-globulin, the clinical symptoms as a whole were significantly less intense The rash developed in less than half of the

TABLE 4 *Development of neutralizing antihemagglutinating (HI) and complement fixing (CF) antibody titers in two children with pre vaccination antibodies before and after inoculation of live attenuated measles virus vaccine*

Child no.	Age	Specimen taken	Antibody titer Neutr	CF	HI
*6	3 month	6 weeks before inocul tion	8	16	20
		At the time of inoculation	<4	8	10
		4 weeks after inoculation	<4	<4	<10
28	2 months	6 weeks before inoculation	32	16	40
		At the time of inoculation	8	8	20
		4 weeks aft inoculation	<4	4	10

children but it was mild of roseola infantum type and in the only child who had a cough this was very slight

Judged by immunological response and clinical reactions, the live attenuated measles virus vaccine used with subsequent gamma-globulin administration seems under the conditions of the study suitable for measles immunization. Without gamma-globulin this vaccine might be valuable under special circumstances. For routine pediatric immunization, however a vaccine giving milder reactions would appear desirable.

Recently Karelitz *et al* [7] have reported the clinical and immunological results of three batches of measles vaccine in children. One of the vaccines (no 3) was the same as used in the present study Their results are very similar to ours. The incidence of fever (94 %) rash (81 %) and cough (37 %) was almost identical. Koplik spots were seen in 19 % compared with ca 35 % *in the present study*

Summary

The clinical and serological effects of an attenuated measles virus vaccine prepared from the chick embryo passaged Edmonston strain and given subcutaneously with or without gamma-globulin has been studied in institutionalized infants and children. Of 22 children vaccinated without subsequent gamma-globulin administration, none had prevaccination antibodies and all developed complement fixing and antihemagglutinating antibodies after vaccination. All responded with fever ranging from 38 0 to 41 4°C. A rash appeared in 19 children, in eight of whom it was generalized and nine children had a mild cough. No complications could be noted in chest X ray examinations or in EEG tracings. No evidence of contact infection in the unvaccinated control group could be observed. A small dose of gammaglobulin given on the fifth day after vaccination to a further 16 children did not significantly depress the antibody response *but considerably reduced* the clinical reactions. Two children of the latter group who still had maternal measles antibodies did not respond clinically or serologically to vaccination.

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(P.H.) Department of Virology
University of Helsinki
Fabianinkatu 24
Helsinki
Finland

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From the State Serum Institute, Helsinki, Children's Castle, Helsinki, Microbiological Laboratory Orion Pharmaceutical Manufacturers, Helsinki, Finland, and Vaccine Laboratory R.I.T Genval, Belgium

Studies on Combined Adsorbed Poliomyelitis–DTP Vaccine

Poliomyelitis Antibody Responses of Children to Primary Immunization

by P. HALONEN, J. KAUHTIO, M. LAMY, K. LAPINLEIMU, K. PENTTINEN, J. PERHEENTUPA, R. TAMMILEHTO and N. TÖRNBLOM

The immunologic efficacy of a combined poliomyelitis diphtheria tetanus and pertussis vaccine has been well described [1–4, 7–9, 11–14]. There are, however, some doubts about the efficacy of the poliomyelitis component after prolonged storage of the combined vaccine, which may be one reason why this vaccine has not yet been recommended by international committees [6].

A further limitation of its value has been the fact that poliomyelitis vaccination is usually begun after the age of 6 months, when the maternal poliomyelitis antibodies have disappeared, whereas DTP vaccinations should be begun at the age of 3 months to enable the child to acquire an early immunity to pertussis. It has been reported, however, that inhibition by maternal antibody of the response to poliomyelitis vaccine can be overcome by increasing the antigenic stimulus [10].

The present report describes the poliomyelitis antibody responses of infants and children to primary immunization with combined poliomyelitis–DTP vaccine adsorbed on aluminum phosphate and stored for 3 to 8 months. These are compared with the responses in infants and children immunized with poliomyelitis vaccine and DTP vaccine prepared from the *same vaccine batches* as the combined vaccine and given in separate injections.

Material and Methods

Design and operation of study. The 90 infants and children with a negative immunization history to poliomyelitis, diphtheria, tetanus and pertussis in five institutions in Helsinki were divided into two groups A and B. The age distribution of the children in the groups is shown in Table 1.

Group A was vaccinated three times at monthly intervals with 0.5 ml of poliomyelitis vaccine and 0.5 ml of DTP vaccine. The vaccines were injected intramuscularly with separate syringes and needles into separate gluteal regions.

Group B was vaccinated according to an identical immunization schedule with 1.0 ml of the combined poliomyelitis–DTP vaccine.

Blood specimens were taken before the first immunization, one month after the

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(P.H.) Department of Virology
University of Helsinki
Fabianinkatu 24
Helsinki
Finland

hours at 36 –37°C and overnight at +4°C One half ml of each mixture was inoculated to two tubes of U-cells (strain Utrecht of a continuous line of human amnion cells) containing 0.5 ml Amino acid Parker" (5) and 2.5 % calf serum. The final microscopic examination of the tubes was done when the corresponding control virus titration showed approximately 100 $TCID_{50}$, usually in 3 to 4 days.

Results

Distribution of triple negative children. The distribution of triple negative children according to the vaccination group and the age of children is shown in Table 2 The term "triple-negative" is used below for the children who were triple-negative either before or one month after the first vaccine injection.

TABLE 2. *Distribution of triple negative children*

Age group	Vaccine group: Poliomyelitis	Vaccine group: Poliomyelitis–DTP
2–6 months	2 2*	12 + 3*
> 6 months	12 0*	9 + 1*
Totals	16	25

The number of children who became triple negative during the interval between the first and second blood specimens. The only case in the group > 6 months old was 8 months old.

Comparison of combined poliomyelitis–DTP vaccine and poliomyelitis vaccine. The poliomyelitis antibody responses to the poliomyelitis vaccine and to the combined vaccine are shown in Tables 3 to 5 and Fig 1 The titers are expressed as reciprocals of serum dilutions

As shown in Tables 3 and 4 the conversion rates of Types 2 and 3 were 95–100 % in each group The Type 1 conversion rates in the poliomyelitis vaccine group was ca 65 %, in the combined vaccine group ca. 80 % In the triple-negative children (Table 5) the difference between the Type 1 conversion rate of the combined vaccine group (ca. 75 %) and the poliomyelitis vaccine (ca 50 %) was even greater

The Type 1 antibody titers were slightly higher in the combined vaccine group than in the poliomyelitis vaccine group (Fig 1) This was especially obvious in children with no prevaccination antibodies. Types 2 and 3 antibody titers in the two groups were approximately the same

Comparison of poliomyelitis antibody responses in two age groups The poliomyelitis antibody responses to the poliomyelitis vaccine and to the combined vaccine in two age groups are shown in Tables 3 and 4 and Fig 2.

The antibody titers of Types 1 and 3 are approximately the same in both age groups among children with no prevaccination antibodies. In the older age group children with prevaccination antibodies responded well to vaccination with two exceptions the titers increased 2 to 128 times

TABLE 3. *Poliomyelitis antibody responses in children after three injections of poliomyelitis vaccine*

Age group	No. tested	Negative to type 1	2	3	Conversion from < 4 to 4 or more: Type 1	Type 2	Type 3
2–6 months	18	1[illegible]	9	11	9/12 (ca. 8[illegible])	9 (10[illegible])	11 11 (100%)
6 months	[illegible]6	15	23	20	9/15 (ca. 60%)	22 22 (100%)	19 20 (95%)
Totals	44	27	31	31	18/27 (ca. 6[illegible])	31 31 (1[illegible])	30 31 (9[illegible])

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(P.H.) Orion Pharmaceutical Manufacturers
Microbiological Laboratory
Nilsiänkatu 10–14
Helsinki
Finland

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From the Children Department and Pediatric Research Laboratory (Head. Professor Leif Salomonsen) University Hospital, Rikshospitalet Oslo.

Observations on the Urine of Asphyxiated and Dysmature Newborn Infants

by SVERRE HALVORSEN and KJELL AAS

Isolated cases with renal lesions fol lowing perinatal asphyxia have been reported in the literature [2, 3 9 10] Otherwise the renal reaction to hypoxia in the newborn period is relatively unknown. This is in part due to the rapid autolytic processes in the kidneys of newborn infants post mortally and routine autopsy material can therefore only disclose those with marked lesions. McCance & Widdowson [11] have performed metabolic and renal function studies on infants born following protracted labor and forceps delivery Their findings indicate that these infants have a greatly increased tissue protein breakdown, an increased phosphate excretion immediately after birth, a low glomerular filtration, a poor urea clearance, a low urine volume and a high ratio of nitrogen/potassium in the urine.

A chance observation of markedly increased amounts of granular casts and renal epithelial cells in the urines of three asphyxiated infants made us examine such cases more closely with regard to kidney impairment. There appeared to be few data in the literature concerning the cellular xcretion in the urine either of nor mal or asphyxiated newborn infants, and the normal excretion pattern had to be established [1] It was early pointed out by German investigators, that uric acid infarctions and uric acid casts were frequently found in infants born after protracted and complicated deliveries [14] In addition to the studies on urinary sediment, other laboratory tests have been included to evaluate the general and the renal reaction to neonatal hypoxia.

In the present study mature infants with perinatal asphyxia and postmature infants have been studied. The findings in these cases are compared with a control group selected on very strong criteria as to a normal labor

Material

Eight infants with perinatal asphyxia but without signs or symptoms of malformations, infection or dehydration were selected. The degree and duration f the asphyxiated state were variable. Some lini cal data are given in Table I

Dysmature infants were also studied. The criteria for dysmaturity were in accordance with those given by Clifford [4] including only those which scored II or more according to his grading

Inf ts f perfectly healthy mothers with uncomplicated pregnancies and uneventful

TABLE 1 *Clinical data on the asphyxiated infants*

Infant	Birth weight g	Description of delivery	Condition at birth	Establishment of *respiration*	Condition during *first five days*	Psycho-motoric development
[illegible]	5 [illegible]60	Protracted labor F tal distress Cesarean section	Asphyxiated Gasping respiration	15 min	Weak. Cyanosis Convulsions	Normal 24 months
Dl.	4090	Fetal distress Forceps delivery	Weak Flaccid	Immediately	Irritable. Weaning Paresis of right facial nerve	Normal 9 months
Eg	3160	Amniotomia Otherwise normal	Asphyxiated	15 min	Weak Grunting	Normal 24 months
Ul.	4000	Protracted	Asphyxiated	12 min	Apnoe. Cyanosis Convulsions	Normal 12 months
Gj	3550	Protracted labor Fetal distress Amniotomia	Asphyxiated	60 min	Cyanosis Convulsions	Normal 14 months
Th.	3200	Neglected shoulder presentation Cesarean section	Asphyxiated	7 min	Cyanosis Opistotonus Convulsions	Normal 4 months (Epilepsy)
Ru.	2990	Fetal distress Forceps delivery	Asphyxiated Intubated	After intubation	Cyanosis Pulmonary rales	Normal 11 months
As.	3380	Spontaneous Uncomplicated	Asphyxiated	7 min	Gradually improving	Normal 24 months

deliveries were selected as normal controls. The neonates were examined by a pediatrician specially associated to the obstetric department as well as by one of the authors. Infants with respiratory distress or with any known pathological trait were excluded. The infants were fed according to modern principles f neonatal care. Only those with a normal weight curve and without signs of unphysiological dehydration were selected as controls.

Because f the more convenient sampling, *male infants* were preferred. One hundred and fourteen male and twenty-seven female infants serve as controls in the present study

W also had the opportunity of observing an infant born to a mother with severe barbiturate intoxication. The mother was hospitalized in poor shape, comatose and with signs of dehydration 3 weeks prior to delivery The delivery was uncomplicated and the infant thrived.

Methods

Sampling of urines, sediment staining and sediment count were performed as described recently by one f us [1]. Specific gravity was determined both by urometer and by the floating drop method, in the smaller volumes with the latter only

The pH was determined by Special Indicator Paper Merck. Protein was determined by qualitative methods only using the HNO_3 precipitation test of Heller and Albustix reagent strips Ames concurrently while glucose and reducing substances were determined by Benedict's qualitative test and Clinistix reagent strips Ames

The amino-acid excretion was determined by two-dimentional paper chromatography using butanol/acetic acid/water as the first solvent and phenol/water as the second. An aliquot of urine corresponding to 0.250 mg N was applied to Whatman no. 1 paper and

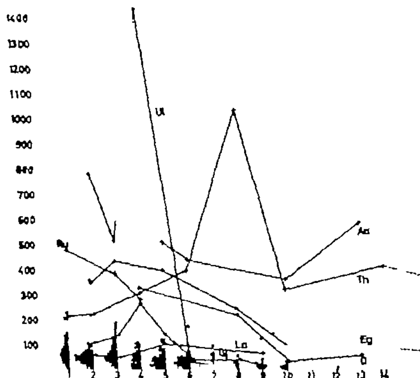


Fig. 1. Total of renal epithelial cells and leucocytes per mm³ of urine. ● = normal controls; + = asphyxiated infant.

the chromatograms were developed with ninhydrin at 80°C for 15 minutes. The spots were enumerated from 0–6 according t size and colour intensity

Blood analyses were performed in capillary blood with micro-methods used routinely in the hospital.

The creatinine tolerance test was done as described by Sundal [18].

Results

Observations on the daily urinary out put and the sediment excretion in the normal infant were published in detail recently [1]. The daily urinary output of the asphyxiated infants a compared to the normal is demonstrated in T ble The sediment excretion of the sphyxiated infants as compared with the control material is plotted in Fig 1 Differentiation was originally attempted by tabulating three categories: (1) "typical non squamous epithelial cells of renal origin (2) typical leucocytes and (3) renal epithelial cells or leucocytes of more un certain structure" It is often impossible to differentiate with certainty between the renal epithelial cells and th leucocytes, and in the figure the totals of the three categories mentioned are plotted. Epithelial cells other than those of assumed renal origin were not counted Erythrocytes and casts were oft n found in abundance in the urines of normal infants during the first week of life [1] In the urines of

TABLE 2. *Volume of urine voided in 24 hours*

Day	1	2	3	4	5	6	7	8	9	10
Normal average...	16.8	34.1	63.8	86.4	125.8	134.8				
Normal range	0–68	0–84	0–71	14–160	44–216	40–200				
La		64	58		82				30+	
Dl				71				208		300
Eg	0	90	48		50+			26+		164
Ul		93		56		240	110+			
Gj			66	60	73	220		16		
Th	14			5..		23+			160	163
Ru	2..		46	123						
Aa					186	1801				246

the asphyxiated infants great numbers of erythrocytes and casts were often but not regularly encountered and were usually close to the upper normal limit A most impressive difference was noted in the appearance of the casts from the asphyxiated infants as compared with those found in the control urines. In the normal urines casts were mostly granular or hyaline with some epithelial cells or cell debris incorporated. Heme casts, broad casts or waxy casts were not observed in these urines In the urines of the asphyxiated infants broad casts were regularly present sometimes in great numbers. Heme casts were found in the urines from three infants and waxy casts in three. (*In two infants heme* casts and waxy casts were present at the same time.) In the urines of the asphyxiated infants the casts were mostly of the granular type or hyaline with large amounts of epithelial cells, some leucocytes and cellular debris incorporated. Epithelial casts and casts containing compressed rows of epithelial cells were not uncommon. In some of the casts doubly refractile fat bodies were observed Changes similar to those in the asphyxiated group were found in the urine of the infant born to the barbiturate-intoxicated mother

The observations on the pH of the urines from normal infants were in accordance with those of others [20]. No difference could be demonstrated between the asphyxiated infants and the controls.

The specific gravities of the urines in the asphyxiated group and the controls are shown in Table 3

The observations on proteinuria and glucosuria are tabulated in Table 4, and observations on amino-aciduria in Table 5.

Some observations on serum NPN creatinine and hematocrit are demonstrated in Table 6

Creatinine tolerance tests were performed in one asphyxiated infant showing a 0 and 30 % *excretion*, while two normal infants excreted 68 % and 75 % of the ingested creatinine.

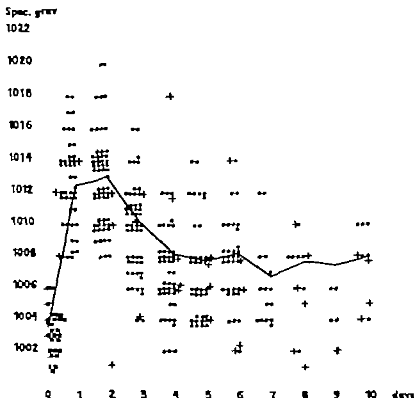
Similar studies were done in a group of 5 dysmature infants (Table 7).

Discussion

Several authors have described renal lesions in newborn infants dying after severe asphyxia. Jonsson [9] described one case with numerous casts in the distal convoluted and collecting tubules and *two other surviving patients* whom he sus-

TABLE 3 *Specific gravity*

– preformed urines; ● – normal controls; + – asphyxiated infants; curve – normal mean.



pected of having "lower nephron nephrosis. Kessel & Pepler [10] described degeneration of the renal tubular epithelium in one case and Bernstein [3] reported three cases with renal tubular necrosis and maintained that the lesions in the kidney were probably due to circulatory disturbances during asphyxia. He also found pancreatic islet necrosis in his cases.

TABLE 4. *Proteinuria and glucosuria*

	No.	Protein	Glucose
Asphyxia	8	6	1 (slight)
Control	141	2	4 (sligh)

Ahvenainen [2] reported two cases with distinct changes in the tubular cells and one case with "slight changes in the

TABLE 5 *Urinary amino acids*

Amino acids	Total	BAIB	Ethanolamine
Normal verage	16.3	1.25	1.6
Normal range	8.5–36	0–4	0–3
La	18.5	0.5	2
Dx	24	1	1
Eg	—	—	—
Ul	27	0	0.3
Gj	10	1	0.5
Th	23	1	3
Ro	31.5	0.5	2
As	6	0	1

TABLE 6 *Hematocrit NPN and creatinine.*

	Hematocr	NPN	Creatinine
Normal average	67	23	0 9
Normal range	57 78	10–59	0 4–1 6
La	59	107	1.4
Di	49–54	150	1.3
Eg		78	0.3
Ul	6.–60–6..	35	1.9
Ol	66	68	1 0
Th	67–60–6	280	2.7
Ru		54	1.3
As	59–61–56	67	1 0

kidney" As most of these infants died within few days after birth, only occasional urine specimens have been examined It is of interest, however that Jonsson s fatal case did not show proteinuria

The urinary findings in cases of acute renal failure in adults are well established [19]. Proteinuria is most intense during oliguria and usually lasts for 1 to 3 months. The specific gravity approaches 1010 during oliguria and in the early diuretic phase In the recovering patients first the diluting and then the concentrating ability develop. Glucosuria is not usual Gross hematuria is common during oliguria later only microscopic hematuria occurs. Leucocytes, renal epithelial cells and casts are sparse during the oliguric phase but increase markedly during the first period of diuresis.

In an outstanding article on the morphology of acute renal failure Oliver *et al* [13] describe scattered patches of tubular rhexis as the most prominent feature. *Rarely is the whole nephron affected*, but only a short stretch of a tubule or series of isolated spots. In these patches the entire wall is affected. The basement membrane may be broken and the epithelium within it may be dead and desquamated, resulting in a disruption of the continuity of the tubule Casts may be seen and they may extrude from the gaping hole in the tubule Leucocytic infiltration commonly occurs around the lesions.

In all but one of our asphyxiated infants the cellular excretion in the urine was markedly increased (Fig 1). While the increase of renal epithelial cells and leucocytes in the sediment was notable the increase in number of casts was less prominent. In all asphyxiated infants as compared with the normals, however the urinary casts were distinguished by appearance and increased amounts of inclusions. The

TABLE 7

Infant	Volume	Sp.gr	Protein	Aminoacids	Casts	Cellular excretion
H.	Low normal	Low normal	+	Normal	Normal	Increased
L.	Low	Elevated	+	Normal	Increased Broad	Slightly increased
F	Low	Normal	+	Normal	Increased Broad Waxy	Increased
A.	Normal	Normal	–	Normal	Normal	Increased
W	Normal	Normal	Trace	Normal	Increased Broad	Increased

This table summarizes the results of the urinary findings in five dysmature infants.

cast, with its measurable dimensions of size form composition and incidence is a readable message from the nephron that formed it" [16] This applies equally well to the urinary sediment as a whole and to each constituting element of it. The observations on the urinary sediment indicate that in the asphyxiated infants an increased desquamation of the tubular epithelium has occurred, and the sediment found is of the type expected in tubulor rhexis.

The observation of increased cellular excretion in the urine of asphyxiated infants has practical importance for the differential diagnosis of pyelonephritis in the newborn period. Sauer [15] described 15 cases with onset of symptoms from 6–28 days after birth without mentioning the birth history and Craig [5] reported pyelitis in several infants who had perinatal asphyxia. In the present study bacteriological studies were not performed routinely but repeated cell counts were performed until the cellular excretion was normalized, and this occurred usually within two weeks. In cases of asphyxia it is therefore advocated to postpone treatment for suspected urinary tract infection until the bacteriology is established and several specimens have been examined.

The problem of proteinuria in the newborn infant will not be discussed here. The finding of fewer cases of significant proteinuria in our control material than is usually reported fits in well with the observations of Doxiades *et al.* [6]. The narrow criteria used and the preponderance of male infants in our study are important factors The demonstration of proteinuria of significant severity in the asphyxiated infants further supports the concept of a renal lesion in these cases.

The specific gravity and the volume of urine in our eight cases do not differ significantly from the control group The increase in cellular excretion is therefore real and can be established when the Addis count in each case is computed. Only one of the infants had a definite oliguric phase as in cases of acute renal failure in older age groups, but as all infants have low urine volumes during the first days this may be difficult to interpret.

Glucosuria is rare in acute renal failure [19] but has been described rather frequently in newborn infants. In our cases only one had glucosuria.

Hyperaminoaciduria has been described by several authors as a relatively frequent finding in acute renal failure [17]. The pattern of amino acid excretion in this disease does not seem to be specific. In the newborn period the aminoacid excretion differs from that seen in older children and adults [7 1] There is then a higher excretion of amino acids than later and the pattern on a chromatogram is characteristic in that ethanolamin (eth.), β-amino-iso-butyric acid (BAIB) proline and hydroxy proline are distinctive spots. In the control group of 24 infants we found this pattern with eth. and BAIB as the most frequent finding Almost all the urines were taken during the first week of life and this may explain why some of the urines had no or only weak spots of proline or hydroxy proline.

In the asphyxiated infants the amino acid excretion was on the average higher than in the control group, but as the excretion in a few of the normal infants was equally high, this is not definitely patholo-

gical. The excretion of eth. and BAIB was less prominent in the asphyxiated infants than in the controls This questions the theory that the high excretion of eth and BAIB in the neonatal period is due to increased tissue breakdown [7] Since the asphyxiated infants have a higher protein breakdown than normal [11] one would expect a higher eth. and BAIB excretion if this theory was correct.

The well known rise in serum urea con centration in newborn infants and especially in those with perinatal asphyxia is explained as mainly being due to increased tissue protein breakdown [11] The con comitant rise in serum creatinine in two of our cases suggests, however that a renal component may also be present. A reduced creatinine tolerance test in one case fur ther supports this view although this test is not very reliable in this age group

The finding of definitely increased amounts of renal epithelial cells, granular and heme pigment casts must be taken as convincing evidence that these infants have a renal lesion, and it may be postu lated that such lesions are common in peri natal asphyxia. We have, however few data on renal function, and the deviations from the control group are small. It is reasonable to believe that the renal lesions are of moderate degree and give rise to only minor and reversible reductions in kidney function. In some severe cases they may however be of greater function al importance and may participate in the nitrogen retention so commonly seen in asphyxiated infants. Several factors may be of importance as causative mechanisms. It is most likely that renal ischemia is the most important one causing tubular necrosis. The electrolyte disturbances and the acidosis which are constant findings in severely asphyxiated infants may in them selves give rise to renal damage and functional disturbances. In adults renal function is diminished with a pH of 7.2, and renal shutdown occurs when the pH reaches 7 0 [8] Dehydration because of poor sucking and small fluid intake is a third important possibility In older children and adults dehydration is one of the most common causes of acute renal failure. Dehydrated infants were excluded from our study however This is also confirmed by the low normal hematocrit levels in our eight reported cases. If dehydration develops this will aggravate the renal lesions, and this seemed to be true in one of the first cases that came to our attention. In our opinion the circulatory failure during asphyxia is the most important factor and the acidosis and/or dehydration may ag gravate already existing renal damage. The observations on the urines of dysmature infants confirm this impression. The urinary findings in the dysmature infants are very similar to those in the group of asphyxiated infants. This is probably because some of the dysmature infants also had perinatal asphyxia and in addition they had varying degrees of dehydration.

McCance & Widdowson [11] described their findings in newborn infants born after difficult and protracted labor as a syndrome. The following should be added to their findings: increased cellular excretion in the urine as an almost constant finding frequently proteinuria and possibly aminoaciduria in some cases.

We feel that serial determinations of hematocrit, blood urea, creatinine and electrolytes together with exact sediment counting of the urine can give a clue to the

degree of perinatal asphyxia and thus may have prognostic value.

The metabolic derangements following perinatal asphyxia may be due to salutary processes and *should in that case be left* undisturbed, but we think it more probable that they represent a further stress on the infant. In newborn pigs McCance & Widdowson [12] have observed that glucose diminishes the protein breakdown. This finding is also well known in adult cases of acute renal failure. It seems reasonable to administer glucose solutions to the asphyxiated infants in order to decrease the nitrogen retention, and at all events protect the infant from dehydration. Tube feeding is essential in the more severe cases, *but on account of the possible renal* lesion the amount of fluid administered should not exceed that given to normal newborn infants if the clinical examination and laboratory data do not suggest dehydration.

Summary

In the present report data on the urinary *sediment and amino acid excretion* in asphyxiated and dysmature infants are presented. The cellular excretion in the asphyxiated infants was markedly increased and broad, waxy or heme pigment casts were *frequent* findings. The dysmature infants revealed similar but less distinct changes. In the asphyxiated infants the total amino acid excretion was higher than the average for a control group but did not show qualitative differences from the normal newborn pattern. Proteinuria was frequent both in the asphyxiated and dysmature infants. Two of the asphyxiated infants had elevated serum creatinine levels and one showed a reduced creatinine tolerance test.

Based on the findings of the pathological sediment *in the urine it is postulated that* renal lesions are common as a result of perinatal asphyxia. The lesions are probably of moderate degree and give rise to only minor reductions in kidney function. Perinatal asphyxia is an important differential diagnosis in cases presenting with pyuria in the newborn period.

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Department of Pediatrics and
Pediatric Research Laboratory
Rikshospitalet
Oslo
Norway

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From the Central Hospital for Infectious Diseases (Director: Dr J Román), Budapest, Hungary

Ventilation Studies in Children of Different Ages

by D BODA and L. MURÁNYI

In general paediatrics has not been able to keep up in recent years with the great advance achieved in the field of pathology of the respiratory organs. Difficulties in the methods are responsible in the first place for the fact that we are still far from being able to use such studies in paediatric practice. Moreover the number of fundamental measurements is remarkably small [5 10 11], a considerable proportion of the published data concerns newborns [1 3 8] and it is still controversial whether the data already available are really and truly established ones. Some of the values were obtained in children under the influence of sedatives while the others were measured during sleep. For this reason it is considered that our studies made by the use of a method described earlier [1] may be worthy of attention. Our method has the advantage of not requiring any particular collaboration by the patient and makes it possible to determine simultaneously a number of the more important data of respiratory function.

Materials and Methods

Our method requires the direct determination of three data. These are: (1) CO production per minute (2) CO_2 content of expired air and (3) the arterial PCO as measured by means of a gastric balloon (gastrotonometry). From these data we can calculate minute ventilation alveolar ventilation, tidal volume dead space and respiratory equivalent. The correlation and the procedure followed in calculation are shown in Fig. 1 in which $\dot{V}_{CO_2}$ is the CO production per minute in ml (STPD), $C_{E_{CO_2}}$ is the CO content of expired air PCO is the CO fraction of gastric air $\dot{V}_E$ is minute ventilation (minute volume), $\dot{V}_A$ is alveolar ventilation, V_T is tidal volume and V is the physiological dead space; R is the respiratory equivalent. The procedure of the test has been described in a previous report [1].

In the present studies a micro gas analyser of Scholander [13] was used for gas analysis. We found the sensitivity of the method to be 0.0[illegible] % CO_2.

The test subjects were eutrophic, symptom free hospital patients who had suffered from some milder illness earlier. The tests were made in the morning between 8 and 10 o clock, after fasting. The gastric tube had been inserted the previous evening. With subjects less than 1 year old, 5 to 7 cg of Noropan (tablet) was administered per os, ½ or 1 hour before testing, as a sedative. The number of the test subjects (boys and girls) totalled 33. The youngest infant was six weeks, the oldest child was 16 years old. Body surface area was computed on the basis of the widely used Du Bois nomogram.

Results

The results are presented in Fig. 2 to 5. The data have been grouped in two ways. The results for volume ($\dot{V}_{CO_2}$, $\dot{V}$ $\dot{V}_A$, V_T

Fig. 1. Calculation of ventilation data obtainable from the CO_2 production per minute, CO_2 of expired air and gastrotonometric PCO_2.

Fig. 2. Correlation of CO_2 production per minute ($\dot{V}_{CO_2}$), minute volume ($\dot{V}_E$) and alveolar ventilation ($\dot{V}_A$) with body surface area. ● $\dot{V}_{CO_2}$, ○ $\dot{V}_E$, ◐ $\dot{V}_A$

Fig. 3. Correlation of tidal volume (V_T) and dead space (V_D) with body surface area. ● V_T, ○ V_D.

V_D) are plotted against body surface area. Correlation corresponding to straight line has been obtained in the double logarithmic system. The correlations may be expressed also in the form of regression equation, the pertaining data together with the correlation coefficients and the scattering around the regression curve are shown in Table 1. According to the value of the cor

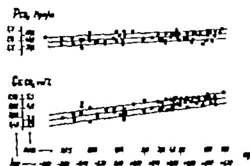


Fig. 4. Correlation of gastrotonometric CO_2 tension (PCO_2) and CO_2 of expired air ($C_{E_{CO_2}}$) with age. ● PCO_2 ○ $C_{E_{CO_2}}$

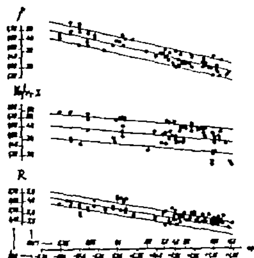


Fig. 5. Correlation of respiratory rat (*f*), percentage dead space (V_D/V_T) and respiratory equivalent (*R*) with age ● *f*; ○ V_D/V_T; ☾ *R*.

relation coefficient the correlations are close enough, especially between $\dot{V}_{CO_2}$, $\dot{V}_A$, $\dot{V}$ and body surface. The smallest correlations were found in the case of $\dot{V}_E$ and V_D. The correlation was similar only slightly smaller when the data were related to body length or body weight.

The other data notably respiratory rate (*f*), the CO content of expired air the PCO_2, the value of the respiratory equivalent and the percentage dead space (V_D/V) were related not to body surface area, but to age Here too the results were plotted in the double logarithmic system. The values for the regression equation and for the correlation coefficient are to be found in Table 1 in the case of this group, too

TABLE 1

	Regression equation[a]	Correlation coefficient	s_y[b]
CO_2 production per minute vs. surface area	V_{CO_2} = 135.63 s.a. [illegible]	0.913	0.078
Minute ventilation vs. surface area	V = 3.793 s.a. [illegible]	0.882	0.098
Alveolar ventilation vs. surface area	V 2.865 s.a. [illegible]	0.899	0.093
Tidal volume vs. surface area	V = 179.0 s.a. [illegible]	0.871	0.111
Physiological dead space s. surface	V_D = 51.29 s.a. [illegible]	0.738	0.148
Gastrotonometric CO_2 tension vs. age	P_{gCO_2} = 4..26 age[illegible]	0.666	0.043
CO_2 of expired air vs. age	$C_{E_{CO_2}}$ 3.530 age[illegible]	0.761	0.036
Respiratory rat vs. age	f 34.79 age[illegible]	0.577	0.053
Percentage dead space vs. age	V_D/V 33.8 age[illegible]	0.384	0.137
Respiratory equivalent vs. age	R = 3.38 ge[illegible]	0.742	0.062

V_{CO_2} ml STPD V_E, $\dot{V}$ =1 BTPS; V_T, V = ml BTPS P_{CO_2} mmHg; C_{CO_2} = vol. per cent; f rat (min), s.a. square meter; age = years.

s_y deviation (scattering) of regression equation.

Among the data those relating to respiratory volumes increased with the increase of body surface. It is to be emphasized, however, that the data for PCO_2 and C_{ECO_2} also depended on age: in early childhood the values were at a lower level than is the physiological normal for adults. In contrast to this, the percentage dead space and the respiratory equivalent values were lower in older age.

Discussion

First of all we must consider the sources *of error of the measurements. Like the* respiration studies in general, ours also yield only approximate results. As regards the fundamental measurements, no allowances had to be made with the determination of $\dot{V}_{CO_2}$, but in the case of expired air we are fully aware of the fact that what we deal with is not truly values for mixed exhaled air. To get that, we ought to have used a valved mask or a mouthpiece, which would have falsified the results. We think that, bearing this in mind, our data can be used. After suitable training the parallel tests yielded closely comparable results. In general, our values for expired air are higher than the ones published earlier. This, too, tends to indicate that our results are more reliable. The body plethysmographic studies in which the composition of expired air was determined indirectly, without the use of a mask on the mouth (oral mask, mouthpiece), yielded results still higher than ours.

As to PCO_2, it is known that by our method we get values 4 to 6 mm Hg higher than the true arterial PCO_2. Nevertheless, we employed no correction although the error is systematic. Owing to its practicability, our method may soon become a standard one and therefore it will be unnecessary to take into consideration the deviation arising from this almost negligible difference. In the old test for arterial PCO_2 blood had to be obtained by arterial puncture. This explains why so few such data have been published and why no large series like ours can be found in the literature concerning PCO_2. Up till now we considered the normal values, independent of age, to be around 38 to 4[illegible] mm Hg. It is now clear that there is a rise in PCO_2, as a rule, with the advance of age. In the younger generations values lower than 40 mm Hg are often found even without correction, while later the values range mostly from 40 to 50 mm Hg, and are more than once higher than 50 mm Hg. Thus, our PCO_2 values are somewhat higher, even if we take into consideration the systematic difference of 4 to 6 mm Hg. We are convinced that in this a role is certainly played by the fact that, as opposed to the values obtained by arterial puncture, ours are for sure resting ones. There are many claims in the literature suggesting that arterial PCO_2 is not so rigidly around 40 mm Hg. Values higher than that are found very often, especially when the conditions of the experiment provide for a complete relaxation and rest of the test subject. Moreover, our studies concerning the diurnal variations have revealed that we selected the period in which the highest PCO_2 values are obtained during wakefulness.

The sources of error mentioned all point in one direction; the values derived can be relied upon excellently in the studies of pathological conditions and by the method

we can measure so many normal children that it is almost unprecedented. Of the relatively scarce pertaining evidence in the literature, those which agree with our results were obtained by devoting special attention to ensuring complete rest of the test subject.

The deviation from the mean of our results is not greater than what is usual with such gas exchange studies. Apart from the almost negligible sources of error the deviations from the "normal" seem to be responsible for the fact that scattering cannot be brought down to a lower level. In spite of the apparently justified criticism of the Du Bois nomogram for body surface area [7] we have got the closest correlation in relation to body surface.

On the basis of similar measurements, Maslov [8] pointed out that even under physiological conditions the infant has to carry out gas exchange under most unfavourable circumstances. Our results, too are illustrative of this. It can be seen that the younger the child, the less favourable are the conditions of ventilation by which the increased metabolism has to be carried out. At a younger age the respiratory rate is higher minute volume is relatively larger and even the alveolar ventilation is greater than, as compared to a later age the young child is hyperventilating This increased ventilation is carried out with a relatively smaller tidal volume, and even the percentage dead space is greater than at a later age. All these add up to make the respiratory equivalent higher at a younger than at a later age which means that to bring out the same amount of CO_2 from the lung more air is required, the respiratory effect is weaker We think our studies have practical significance in that they permit a deeper insight into the ventilation as it is in infancy and childhood and furnish at the same time a basis for comparison in studies on pathological conditions.

Summary

The principal data of ventilation ($\dot{V}_{CO_2}$, $\dot{V}_E$, $\dot{V}_A$, V_T, V_D), the CO_2 of expired air the gastrotonometric arterial PCO_2, the respiratory equivalent and the percentage dead space values are presented, on the basis of measurements made in 83 normal children of different ages. The values are analysed statistically grouped according to body surface area and age respectively The results permit one to gain an extensive insight into the mechanism of ventilation in infancy and childhood and furnish at the same time a basis for comparison in studies on pathological changes.

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Central Hospital for Infectious Diseases
Gyáli-ut 5–7
Budapest IX
Hungary

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From the Departments of Bacteriology (Head: Prof. R. Grubb) and Paediatrics (Head: Prof S. Sl), University of Lund, Sweden

Insulin Antibodies in Juvenile Diabetes

by GUNNAR ENGLESON and STIG-BERTIL NILSSON

It is a well known clinical fact that in diabetes mellitus there is sometimes a sudden deterioration in the diabetic condition with a high insulin requirement.

In such cases the term insulin resistance has been used. Generally the insulin requirement amounts to 200 IU or more.

Investigations by Berson *et al* [3], among others, have shown that such cases of insulin resistance might be combined with the presence of insulin antibodies. These antibodies have been described as insulin neutralizing or insulin binding" antibodies

The natural course of juvenile diabetes is characterized by a favourable post-initial phase lasting from 1–3 years Gradual intensification of the diabetes then often follows with an increase in insulin requirement to 80 IU or more The diabetic condition becomes more unstable and the tendency to ketosis is more pronounced. In some cases this change in the diabetic course depends on the occurrence of acute infections in other cases the reason is poor diabetic control, but in some patients there is no obvious explanation for the impairment in the diabetic state

With reference to the relation between insulin antibodies and insulin resistance we have investigated 20 cases of juvenile diabetes with due regard to the presence of insulin antibodies as a possible explanation of the above-mentioned deterioration in the diabetic condition.

Material and Methods

The material consists of 39 cases of juvenile diabetes, 17 boys and 22 girls, aged 1½–15 years, all of them treated at the Paediatric Department, Lund.

In 20 cases the examination of insulin antibodies has been performed as well in the initial diabetic state as later on at one or several occasions. In 7 of these there have been a deterioration in the diabetic course

Our material also includes 19 patients with a longer diabetic duration. In these cases as rule only one examination has been made. There is no case of true insulin resistance among the patients.

Serological examination

Phosphate buffer

Phosphate buffered saline pH 7.2 (2 parts 0.85 per cent saline – 1 part Sörensen phosphat buffer = 15) was used as a diluent.

Normal Rabbit Serum (NRS)

Blood from rabbits was taken by venopuncture The sera were collected and inactivated at 56°C for 30 minutes The sera then were absorbed for 1 minutes t room temperature (18°C) against an equal volume of packed three times washed sheep erythrocytes.

Insulin preparations

Pulverous crystalline beef insulin (Vitrum AB Stockholm, Sweden) was used as antigen. The powder was dissolved in a small amount of 0.003 *M* NaOH and diluted with phosphate buffer in order to contain 1 mg insulin/ml, *e.g.* 25 IU/ml. The dilution was always done immediately before use.

Sera from diabetic patients

Blood was taken by venopuncture without anticoagulant. The sera were collected and inactivated at 56°C for half an hour after which the sera were absorbed for 15 minutes at 18°C against an equal volume of packed sheep erythrocytes.

Method

Boyden's technique [4] as applied to the detection of insulin antibodies by several investigators [2, 11] was used with some modifications. Sheep red cells were washed three times in phosphat buffer and treated for 10 minutes at 18°C with a fresh tannic-acid solution (5 mg per 200 ml buffer Merck) The erythrocytes were then washed twice in NRS diluted 1/100 in buffer after which the antigen was added. The proportion between the red blood cells and the antigen was 1 80

The system was standing for 15 minutes at room temperature (18°C) and then the erythrocytes were washed in NRS 1/100 two times. The sera to investigate were diluted 1/5–1/80 with NRS 1/100 as a diluent, whereafter the coated blood corpuscles were added. As a control, sera and tannic acid treated sheep erythrocytes, buffer and antigen—coated sheep red blood cells were used. Furthermore in all the test we used an agglutination-inhibition system, as described by Stavitsky & Arquilla [11], where 0.125 ml serum and 0 125 ml antigen were standing for 30 minutes at 18°C before coated red blood cells were added. The results were read after 2 to 3 hours at 18°C The highest dilution where agglutination was to be found was taken as the titer Absolutely negative controls have been a *conditio sine qua non* for the tests t be estimated. In our material the sera from 5 diabetic children had an antibody titer against insulin antigen. One hundred sera from patients with various diseases have all been negative.

Results

In 5 of the patients investigated there was a positive reaction with regard to insulin antibodies, the titer varying between 1 20 and 1 40 These patients are described below

Case 1

J.B 6-year-old girl. Diabetes at age 5, when determination of insulin antibodies was negative. Her initial insulin dose was 8 IU Lente. After 5 months diabetic duration her diabetes deteriorated. The insulin requirement increased to 20 IU and insulin antibodies were now detected, in a titer of 1:20 The girl was treated with diet, insulin and DBI and afterwards the insulin dose declined to 2 IU Lente Re-examination after 6 months revealed a negative antibody response.

Case 2

M.L. 11 year-old girl, whose diabetes started at 8 years of age. No insulin antibodies were then found. Initial insulin dose 8 IU Lente. During the following 2 years the insulin requirement gradually increased to 16 IU then rather suddenly to 24 IU Now insulin antibodies, in a titer of 1 40, could be shown. Treatment with DBI stabilized the diabetes on a final dose of 20 IU

Case 3

A.A. 15-year-old girl. The patient diabetes made its first appearance in 1957 at 10 years of age, when no insulin antibodies were found. Insulin dose 32 IU Lente. During the following year 1958, the patient had keto-acidosis on several occasions. The insulin dose had to be increased t 48 IU In January 1959 her insulin requirement amounted to 80 IU and now insulin antibodies were found in a titer of 1 20. Later on the patient was stabilized on 48 IU Lente

Case 4

M.G. 15-year-old girl. When her diabetes started, 1956, at 10 years of age no determination of insulin antibodies was made. Initial insulin dose 20 IU Lente. During the following year 1957 the patient had recurrent keto-acidosis. Insulin dose 24 IU. In February 1958 the patient was treated at the Paediatric Department, Lund for ketosis. Now estimation of insulin antibodies was negative. One month later the patient was again referred to the Paediatric Department on account of ketosis, high urinary glucose excretion and increased insulin requirement. Now insulin antibodies could be demonstrated, in a titer of 1:20.

Case 5

G.L. Boy born 1947. Diabetes started in 1951 at 4½ years of age. The patient was treated at another hospital until 1953 when he was referred to the Paediatric Department, Lund. Insulin dosage 24 IU Lente and 12 IU Semilente. During the following years the insulin requirement rose to 60 IU. Cataracta diabetica was detected 1958 and operated upon 1960. In 1961 the patient was treated at the Paediatric Department for general check up. Now for the first time determination of insulin antibodies was made, with a positive result, titer 1:40.

Discussion

Many causes for the high insulin requirement in the insulin resistant cases have been discussed in the literature, for example the enzyme insulinase which can destroy the physiological activity of insulin *in vitro* [7] and *in vivo* [8], antibodies against insulin, and during the last time other insulin antagonists [12]. Several different methods to demonstrate insulin antibodies have been used as well *in vivo* tests—mouse convulsion assay procedure [9]— as *in vitro* tests—glucose uptake in isolated rat diaphragm [5, 14]. Serological methods have been of value to demonstrate antibodies against insulin. Thus Wasserman *et al* [13] in sera from rabbits immunised against insulin have been able to detect antibodies with the complement fixation test. After pre treatment with bis-diazobenzidine or tannic acid red blood cells coated with insulin might agglutinate when sera from insulin immunised rabbits [1, 8] or diabetic patients [1, 15] are added. The investigations of La Presle & Grabar [6] and Scheiffarth *et al* [10] show that the tannic acid method must be judged with reservation, as an impurity in insulin preparations might give a positive result. Sera from patients with different diseases might also give false positive results. With our technique there has not appeared the unspecificity as has been pointed out by Scheiffarth *et al* [10].

La Presle & Grabar [6] found in main that amorphous insulin preparations contain an impurity while crystalline insulin which we used did so just by exception.

Even if it is not probable it cannot be excluded, that the crystalline insulin used by us, contain antigenic impurity.

Of the 5 cases with insulin antibodies earlier mentioned, Case no. 5 differs from the other 4 patients. This patient was first investigated after 10 years diabetic duration.

Three of the cases were new detected diabetics while the fourth patient had a diabetic duration of years. In all these four cases there seems to be a connection between a deterioration in the diabetic condition and the presence of insulin antibodies. None of the patients however showed any signs of insulin resistance. Afterwards their diabetes could easily be controlled.

In the remaining patients with recent diabetes no insulin antibodies could be detected. The same holds for the patients with long diabetic duration. Excepting Case 5 all sera from these patients were negative with regard to insulin antibodies.

The material includes a total of 7 patients with a rather recent diabetic onset, who all had an impairment of the diabetic condition. They were all again referred to the Paediatric Department for investigation. In these 7 cases are included the above mentioned 3 patients (Cases 1 2 and 3) where insulin antibodies could be demonstrated.

The investigation has shown that the occurrence of insulin antibodies in juvenile diabetes is uncommon. It seems to be most frequently seen in recent diabetics In certain cases the presence of insulin antibodies appears to be the only possible explanation of a deterioration in the diabetic condition.

We have had no case of true insulin resistance. There has been no therapeutic problems in the patients with positive antibody response

The occurrence of insulin antibodies appears to be of no practical importance in the course of juvenile diabetes.

A deterioration in the diabetic course seems more likely to be connected with some other type of insulin antagonism.

Summary

At the Departments of Bacteriology and Paediatrics University of Lund, 39 juvenile diabetics have been investigated with regard to the presence of insulin antibodies. Half of the material were patients with recent diabetic onset and the rest diabetics with longer diabetic duration. In 7 patients there was a deterioration in the diabetic course. In 3 of these cases insulin antibodies could be detected. Insulin antibodies could be demonstrated in a total of 5 of the 39 patients. The occurrence of insulin antibodies seems to be of no paramount significance in the course of juvenile diabetes. In a few cases, however the demonstration of insulin antibodies seems to be the only detectable explanation for a deterioration in the diabetes. Other types of insulin antagonism appear to be of greater importance

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Paediatric Clinic
University of Lund
Lund
Sweden

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CASE REPORT

Progeria

by TORGNY DJUPESLAND

From the Children Department (Head: Arnljot Drabløs), Fylkessjukehuset, Ålesund Norway

Progeria is a disease of rare occurrence only about 35 cases having been described since 1886

All progeria patients have a characteristic, uniform appearance with similar course of the disease At birth the appearance is normal, though the weight is usually below the average Among 17 patients with known birth weight, the average was 2680 g The development seems to proceed normally during the first year except that the height and weight remain at the lower limit of normal. But after the first year there occurs a marked retardation in the increase of weight and length, the patient seldom exceeds 15 kg and 110 cm [3]

Arteriosclerotic changes may appear by the age of five years. Death is usually caused by myocardial infarction, which has been reported as early as the age of seven [13] Twelve patients with known length of life showed an average of 13 years, one patient has lived to the age of 26 years [8]

Usually by the age of three years the disease is completely developed, and then the patient has a striking appearance with almost total alopecia protruding eyes a beak like nose hypoplastic mandible and prominent scalp veins. Subcutaneous fat is poorly developed, and the skin is thin and atrophic, often with areas of yellowish brown pigmentation, scleroderma may occur in some cases and the nails are short and atrophic Moderate contractures of the joints often develop

The intelligence is normal, and there is no indication of any senile mental changes.

X ray examination reveals coxa valga. The development of osseous nuclei usually corresponds to the age [1 2, 4, 1., 13]

Pathologico-anatomical examinations have been carried out in 7 cases [2 5 6, 8, 10 12 13] Arteriosclerosis, especially in the coronary vessels appears frequently In the endocrine glands some minor abnormalities have been found, but no constant pathological features have been demonstrated.

As patients with progeria have very little subcutaneous fat and acquire arteriosclerotic disease much interest is focused on the lipid metabolism. Keay *et al.* [7] report elevated cholesterol level in several patients. They stress the elevation of the ratio of total cholesterol to the total circulating phospholipids and the abnormally high concentration of cholesterol in the beta-lipoprotein fraction. This is a

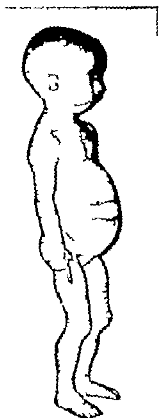


Fig. 1

pattern similar to that of an adult with coronary sclerosis. Rosenthal *et al.* [12] demonstrated an elevated concentration of lipoprotein in the serum and a remarkably high atherogenic index in their patient.

The function of the endocrine glands has been tested in several cases but no consistent abnormality is reported.

Case Report

The patient was a full-term female infant weighing 3123 g. She was breast fed for 8 months with appropriate addition of vitamins A, D and C. Both parents are healthy and not related. A sister six years older is healthy. Dwarfism is not known in the family.

Ever since birth growth has been retarded. At the age of 4½ months the child was 58 cm long and weighed 5430 g. During her first year the length and weight were about 3 percentiles for the age but then there occurred a marked retardation in increase of weight and length. From one to three years the weight only increased from 7240 g to 8500 g, length from 65 cm to 79 cm. When about seven months old, she started to lose hair until at the age of one year she was almost bald. The first tooth appeared at the age of one year. The mental and motor development have progressed normally.

She was brought to the clinic at the age of three years two months (Fig. 1). Length 79 cm (96 cm is the normal average). Weight: 8310 g. Head circumference: 47 cm. Height when sitting: 46.3 cm. She was almost bald with scanty eyebrows and no body hair. The eyes looked protruding, the nose was small and pointed. The ears lacked lobuli and tragi. The mandible was hypoplastic, the palate high and narrow, the teeth standing dense and crowded. The large fontanelle was open, 5 × 4 cm, as was the saggital suture and the posterior fontanelle. Subcutaneous fat was very poorly developed, most of it present in the cheeks and the pubic region. The skin was thin and atrophic with yellowish-brown pigmentation on the abdomen. The veins were prominent, particularly over the cranium. There was a flexion contracture of 15 degrees in both knee joints.

X-ray examination: bilateral coxa valga, thin calvarium with open fontanelles and sutures, normal sella turcica, normal development of osseous nuclei. Ophthalmoscopy: Normal findings. HR 110/80. IQ 140.

Laboratory findings. The following tests were carried out without revealing any deviation from the normal: SR 5 mm. Hemoglobin concentration: 13.9 g%. Urea in blood 39 mg%. Alkaline reserve 61 vol%. Ca 11.5 mg%. P 4.2 mg%. Alkaline phosphatase 3.6 Bodansky units. Cl 103 mEq/L. Na 142 mEq/L. K 5.1 mEq/L. Total serum

TABLE 1 *Analysis of serum lipids*

Date of examination	25 11 1959	9 12.1959	4.2.1960
Cholesterol, mg/100 ml	326	233	344
Phospholipids, mg/100 ml	215	—	270
Fatty acids, mg/100 ml	45	—	133
Neutral fat, mg/100 ml	154	—	172
Total lipids, mg/100 ml	760	—	920

proteins 6 7% with slight increase in alpha, and beta-globulin content and a slight diminution of gamma-globulins. Serum PBI 4 4 μg%. Urinary 17 ketosteroids: 0.7 1 0 mg/24 hours. Urinary 17 hydroxycorticosteroids: 2.9–1 9 mg/24 hours. ACTH test (10 units Jaton prolongatum twice a day during 48 hours) Urinary 17 hydroxycorticosteroids before ACTH 1 9 mg/24 hours; after 4 hours with ACTH: 3.5 mg/24 hours; after 48 hours with ACTH: 9 9 mg/24 hours. Urinary gonadotrophins: FSH, 28 mouse-units/24 hours; LH, less than 7 mouse-units/24 hours. Later two additional controls of urinary gonadotrophins showed FSH and LH-excretion less than 5 mouse-units/24 hours. Glucose tolerance was normal. Urinary amino acids were normal.

The cholesterol content was above the average for the age, the serum lipids were within normal limits as well as the ratio of total polyene acids to total serum fatty acids (Tables 1 and 2)

Skin biopsy: Normal epidermis. Corium consisted of collageneous tissue with few cells. Hair follicles were atrophic, but the erectores pilorum muscles were large and conspicuous, a peculiarity also observed by others [7 12]. Fifty per cent of the cells were sex chromatin positive

Examination of 52 metaphases from a short term bone-marrow culture showed 45 cells with 46 chromosomes, deviations from 46 may be due to technical errors. Analysis of 9 cells revealed a normal female karyotype.

Treatment. The patient was treated with anabolic steroids for 1½ years. The rate of growth of height and weight seemed to increase but no final conclusion should be drawn from this relatively short observation period No side effects were noticed, and the development of osseous nuclei appeared normal during the treatment.

Comment

Mostafa & Garb [9] have described two sisters with progeria, whose parents were first cousins. This is the only indication that a hereditary factor (recessive gene) may be involved in progeria In our case chromosome analysis of other tissues than the bone marrow has not been possible. The finding of a normal chromosome complement in the bone marrow do not exclude the possibility of mosaicism with an abnormal karyotype in other tissues.

TABLE 2 *Analysis of serum fatty acids*

Date of examination	Cholesterol mg%	Total fatty acids mg%	Percentage of polyene acids from total fatty acids					
			Hexa	Penta	Tetra	Tri	Di	Total polyene
9 1.1961	165	370	2.2	2.3	4.0	2.0	22.1	32.6
8.2.1961	203	384	2.9	2.4	4.8	2.3	18.1	31.5

Thomson & Forfar [14] give a review of findings which may indicate endocrine disorders in progeria. The tests carried out in our patient do not indicate any disturbance of the endocrine functions. Several writers [7, 9, 11, 12, 13] find little evidence of endocrine dysfunction and suggest an inborn error of metabolism as cause of progeria.

All patients with progeria have a striking similar appearance. They have malformations (coxa valga) and disturbance in fat metabolism with paucity of adipose tissue, elevated cholesterol level in serum and arteriosclerosis. All these facts strongly suggest a genetic disorder.

Summary

A short survey of progeria is given, and a typical, female case of progeria is described. There are no indication of endocrine dysfunction. The serum cholesterol level was found to be above the average for the age.

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Department of Pediatrics
Ullevål Sykehus
Oslo
Norway

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REVIEW ARTICLE

Infantile Cortical Hyperostosis

A Review with Illustrative Case Report

by WILLIAM COCHRAN

Royal Belfast Hospital for Sick Children

Recognition that a condition of diaphyseal hyperostosis, preceded by soft tissue swelling and associated with constitutional upset, existed distinct from bone syphilis, was first declared by West & Barlow [51] at a meeting of the London Clinical Society in April, 1888

Following the next description by Roske in 1930 [35], sporadic and isolated reports of unexplained non luetic "hyperplastic periostitis" were scattered through major European publications over the next fifteen years [16 23 28 30 47]

The syndrome acquired real definition and prognosis in 1945 from the independently recorded and well-documented series of Caffey from New York and Smyth from California and it is fitting that the accepted eponymous description couples their names. From the outstanding radiological characteristic Caffey called the condition "infantile cortical hyperostosis" Since then an occasional familial incidence has been described [3 27 50 51] and the course has been shown to be not invariably benign by the demonstration of a small associated mortality [17 29 32 41 50]. Confusion with the bone manifestations of chronic Vitamin A intoxication was dispelled at the beginning of the last decade (Caffey [10]) and more recently the clinical and radiological resemblance to vaccinia osteomyelitis has been pointed out by Elliot [22].

Today it should be appreciated that this is an uncommon, but by no means rare disorder of infancy which may present itself in the province of almost any medical or dental specialty concerned with the management of infants It demands watchful support over many months and occasionally claims life yet it may be readily diagnosed by informed appraisal of the whole clinical picture.

Of over ninety cases which have been reported from places throughout the world, two have arisen in Ireland as did the illustrative case described below

Case Report

A previously thriving, female firstborn developed tender bilateral facial swelling of sudden onset, preceded by pharyngitis and irritability and was suspected by a paediatrician to have mumps.

The facial swelling subsided in a week, but after five, further uneventful weeks the



Fig. 1 The facial appearance conferred by hyperostotic expansion of the mandible.



Fig. 2 Exuberant hyperostosis of the left femoral diaphysis.

middle of the left thigh swelled abruptly and she was referred for a surgeon opinion t the Royal Belfast Hospital for Sick Children.

The middle of the left thigh was expanded by distinct tender mass X-ray showed



Fig. 3 Hyperostosis of mandible (and clavicles) about the same time as Fig. 1

layered, sub-periosteal new bone along the entire femoral shaft mushrooming int the soft tissue shadow of the aforementioned swelling (*Fig. 2*).

On account of the ominous inference drawn from this picture the thigh was explored next day revealing invasion f the substance of the vastus intermedius muscle by an adherent non-encapsulated, constantly firm tumour with an irregular bony core It was not unduly vascular and without foci of necrosis. The mass ppeared to arise from periosteum, which merged into it t its edge After removal f material for culture and histology the wound was losed. At the close f the operation the anaesthetist drew attention to the remarkable bony enlargement of the mandible. The relevance of the preceding information now f ll into place and a diagnosis of infantile cortical hyperostosis was made and subsequently confirmed by radiological disclosure f hyperostoses f mandible and clavicle (Fig. 3) in the bsence of vaccination and serological evidence of syphilis. Dr



Fig 4 Microscopic appearance of tissue taken from the mass in the left thigh. Islands of new bone set in cellular fibrous tissue in relation t an atrophied muscl bundle

Ingrid Allen contributed the f llowing pathology report

Histology The biopsy has a varied histological pattern. Sheets of vascular and cellular f brous tissue are broken up by islands f bone. The bone varies in age; in some areas osteoblastic activity is intense and the trabeculae pale staining and ill defined Elsewhere the bone is mature and osteoblast are not so numerous. The related periosteum is thickened and cellular Very few osteoclast are present. The surrounding muscle is atrophic but is not inflamed and sarcolemmal prolifera tion is not pparent. Th muscle bundles are separated by bands of fibrous tissue and immature bone which extend from the thickened periost um. The blood vessels are not inflamed or thickened (Fig 4)

Comment: The marked periosteal thickening intensive fibroblastic act vity and wide spread ossification are the striking features in this biopsy The extension f fibrous and ossification into the surrounding muscle is characteristic f infantile cortical hyperostosis.

Steady post-operative progress was tran siently interrupted on the tenth day by a swelling on the ulnar side f the left forearm —diffuse, firm, tender and just perceptible—whi h came up overnight and disappeared in the course of twenty four hours. There was no systemic upset, but her weight trend, which was steadily rising from operation, dropped 142 g over the next four day before resuming a steady increase and a peak of 38.5 C marked that day on her chart above a plateau f around 37.2 C, which had hith erto been characteristic f the period of hospit l observation.

She was discharged home on the seventeenth post-operative day and continued to progress uneventfully there receiving only oral iron as treatment In the course of out patient surveillance eight weeks after the appearance of the forearm swelling clear-cut hyperostosis f the left ulna was demon strable, though in this instance not nearly so exuberant as the earlier examples elsewhere.

There were no further episodes. Haemoglobin rose steadily to normal levels and weight gain was normal. Swelling of the jaw and thigh receded steadily with parallel radiological recession. Thirteen months from the onset f the illness there was scarcely trace f past hyperostosis on the femur and the jaw was restored t normal—or just possibly a little thickened (Figs. 5 and 6) She is now a thriving child with normal skeleton, dent tion and blood picture

Comment

The features here are typical of the disease as reported. Resemblance to mumps has elsewhere given rise to misdiagnosis in the initial stages [15]

A non uniform cyclical pattern is discernible, with a phase of activity variably marked by constitutional upset, lasting at longest a month and followed by a symptom free period of resolution. The total duration of signs in this case extends to over one year

Whether the preceding pharyngitis is significant is doubtful Similar signs have been noted by others [1 18, 30]. Only during the first six weeks or so was there a



Fig. 5.



Fig. 6

Figs. 5 and 6. Stat of almost complete regression t normal after thirteen months from onset

leucocytosis; later blood pictures were within normal limits for the age, except that the ESR, reflecting the phases of activity took more than six months to return to normal Weight at no time fell outside normal limits.

There ppeared to be no real indication to transfuse blood after operation (though this would have been done prior to opera tion had we not misled ourselves as to the true state of anaemia).

Corticoids were held in reserve. In a situation of steady progress there was no compelling indication to invoke their benefits or invite their hazards

In the pregnancy itself, only the possibility of forceps trauma, significance of terminal t xaemia and the use of a pitocin drip were noteworthy Neither then, nor in the preceding ten years, was the mother known to have been exposed to viral or streptococcal infection or given drug therapy There was no suggestion of familial disease and the parents teeth were

TABLE 1 *Paraclinical data.*

Stage	Weight (birth wt. 3,600 g)	Hb (HEL)	WBC	ESR (Wintrobe)
6th week (age 3½ mths)	5,190 g (Lower end normal range)	8.1 g 55 %	19,500	54
15th week (age 5½ mths)	6,300 g	10.7	13,400	45
26th week (age 8 mths)	8,790 g	12.8	12,800	15
60th week (age 13½ mths)	10,590 g	13...	10,900	6

Platelets Normal. *Capillary fragility test* Negative. *Eosinophils* Not raised.
Culture of biopsy tissue. N growth, aerobic and anaerobic.
Plasma proteins 7 6 g %. Relative increase in alpha-2 globulin, otherwise normal electrophoretic pattern.
Serum calcium. 10.4 mg %. *Serum phosphorus* 7 4 mg %. *Serum alkaline phosphatase*. 37 King-Armstrong units. *Serum carotene* 90 mg % (normal range 60–200 mg %).
Wassermann and Kahn Reactions Unequivocally negative.
Virus complement fixation (psittacine/L.G V group) Negative.

Mother
Virus complement fixation (psittacine/L.G.V) Equivocal (*0/7/60), negative (11/8/60).
Toxoplasma Dye test positive 1 8; comp. fixn. 1 4 (neither significant).
Wassermann. Equivocal. *Kahn*. Negative *Richard potentiation*. Negative

sound The household water supply con tained "nil parts per million of fluorine " (Where Northern Ireland s only other reported case arose, the public water con tained under 0 1 mg per litre)

Discussion

The accepted name for the disorder is misleading if taken to imply that the disease commences solely in infancy It has been spotted radiologically in the unborn foetus, independently in Scotland and California [3 4] An advanced state of hyperostosis and even tibial bending has been present at birth [27 47] The process must begin, at times, at least as early as the twenty-eighth week of pregnancy but at no time has any reflection of active foetal disease been detected in the mother There is no consistent association of hyd ramnios or Rhesus incompatibility

More commonly it presents itself during the first five months of post-natal life. A thriving infant becomes irritable espe cially when handled. Local manifestation in the form of deep tender soft tissue swelling appears within a few days, gene rally but not invariably with febrile ill ness. Most commonly this is in the lower jaw (80 %) with facial swelling. Alterna tively limb long bone involvement may be present with pseudoparalysis, or the chest wall with, occasionally pleural effusion [9] or the scapular region with eventration of the diaphragm [13 14]. Sometimes, however these initial features are so slight as to escape detection.

Shuman s description of the *swelling* at this stage as "brawny oedema while pathologically not exact, does convey a clear impression of the nature—non-pitting, non hyperaemic, non-suppurative

TABLE 2. *The diaphyseal hypero-*

	Infantile cortical hyperostosis	Vitamin A intoxication	Vaccinial osteomyelitis
Onset	Before age of 5 months	Long latent period after 6–12 months	10–14 days after vaccination
Hyperostoses 1	Mandibular involvement in the majority	Mandible and face never involved	N recorded mandible involvement. Skull has been affected
2	Clavicles, scapula, ulna and femur most commonly affected	Never affects scapula but often metatarsals	Scapula one of most frequently affected bones. Also most long bones and metatarsals
3	Never involves metatarsals		
Fever	Nearly always present and protracted	N fever	Fever usual but not invariable
Leucocytosis	Moderate elevation	N	Not marked feature
Demeanour	Hyperirritability	Hyperirritability	Little irritability
Soft-tissue lesion	Large and tender at onset. Never suppurates. Rapidly attains maximum size	Slightly tender N suppuration	May be moderate soft tissue swelling. No suppuration
Hair	Normal	Sparse	Normal
Liver	—	Hepatomegaly	—
Pruritis	None	Present	None
Blood chemistry	Serum alkaline phosphatase alone raised	Raised serum Vitamin A and carotenoids	Raised serum alkaline phosphatase
Anaemia	Usual, may be marked	Not feature	Common, but not severe

Sources: Knapp & Wilson [43], Caffey [12]

firm and tender During the few days it lasts systemic upset is variable and not necessarily related to the size of the swelling There is characteristically no great interference with thriving

A variable degree of hypochromic anaemia progresses to reach its lower limit by the next stage—the stage of radiologically demonstrable hyperostosis which is prominent in about ten days from the subsidence f the soft tissue change

Vigorous and profuse diaphyseal new bone formation gives rise to secondary swelling of quite a different character In the mandible this expansion forms characteristic facies, conferring a "family resemblance" within each ethnographic group (Fig 1) The swelling owes its prominence only to its bulk, for in spite of con tiguous trophy wasting of the whole related muscle bulk is not encountered Tenderness is undoubtedly present, but it is doubtful whether spontaneous pain is to any extent responsible for the occasional persisting irritability indeed this may be a feature of the next cycle, as fever may

stoses of infancy — differentiation.

Congenital syphilis	Pyogenic osteitis	Ewing syndrome	Traumatic periostitis*
1st–30th month	Any time during the entire period	Any time during the entire period	Any time, but most marked in first ten days
Mandible may be in volved, but not fre quently	Mandibular involvement frequent, but usually de structive		
Tibia, femur and hu merus most com mon All metatarsals may be affected	May affect any bone in cluding metatarsals and metacarpals	Selects long bones	Extension from principally meta physeal lesion
Fever not usual	Fever usual, may be pro nounced	Fever usually a marked feature	Little or no fever
No	High polymorph. Leucocy tosis usual	Usual	N
Not disturbed	May exhibit surprisingly little irritability	Irritability not marked feature	Not usually dis turbed
N soft swelling as sociated	Often presents itself in an abscess	May be very prominent and progressive	Initial bruising
Occasional alopecia	Normal	Normal	Normal
May be associated hepatomegaly	N involvement	Liver involvement not usual	Not involved
None	None	None	None
Normal	Normal	Normal	Normal
Not associated	Moderat	Progressive in late stages	Not associated

also be. Some softening does occur as witness the anterior bowing of the tibia noted at this stage [27 47 48]. There is scant X ray evidence of endosteal accretion advancing on the marrow or of rarefying change in the underlying bone, though Eversole describes absorption [24] Absorption is, of course marked in one chronic form (Caffey [12])

Each cycle occupies three to four weeks from abrupt soft tissue swelling to the peak of new bone deposition. This bone is then absorbed, without symptoms in a time purely related to its mass. Total duration varies from three months [?6] to many years [1*] but the average time is about one year

Fortunately for the majority this is the end of the trouble, but for a few there are further complications

Complications

Ensuing complications fall into four categories;

(1) Bone deformity may take the form of anterior tibial bowing appearing early

in the disease. In a later form contiguous bones may be joined by compact non cavitated bridges or the expanded bone of the early stages may persist to become hollowed out to shell thin walls round a dilated marrow cavity [1*]. It is reassuring to learn that mandibular involvement has negligible effects on teeth formation or occlusion, and the prolonged pyrexia no effect on the enamel [5].

(2) A chronic course of recurring swelling and hyperostosis has been largely en countered in Caffey's massive experience [11]. The ultimate outcome is not known some cases are still active after seven years.

(3) Intercurrent infection from lowered resistance may lead to death [29 30]

(4) Sudden death may occur for reasons as yet unknown [17 32 41].

Ætiology

Sex climate season, race geographical location, parental age or placing in family are not significant

The discovery of infantile cortical hyper ostosis in a foetus in utero [2 4] confirmed de Toni earlier suspicion of antenatal origin [4]. This evidence does not how ever prove that the disease invariably commences before birth, for more fre quently the earliest signs have been re ported as arising around the second month of post natal life nevertheless it does suggest that the causal agent or process is capable of crossing the placental barrier and exploiting individual inherent sus ceptibility. Such an inherited tendency is demonstrated in cases where the disease has affected siblings [3 50] mother and child [*7] and father and child [51]. No acceptable case has been described com mencing after five months of age

The mechanical and vascular hypothesis of Barba et al [3] (embryonal dysosteo genesis at the third month of foetal life) obviates the need to invoke an agent, while being consistent with familial mani festation. They note that the common sites of affection approximate to the centres of ossification of the nine week foetus when there is marked growth and differentiation of appendicular muscle with limb rotational changes. In consequence there may be distortion of the diaphyses cutting down blood supply to sites of perichondral bone formation and thereby leading to endost eal bone formation bizarre in form and showing its inadequacy to withstand the strains exerted upon it by a proliferative response. Variations in blood supply around the threshold of adequacy would produce lamellation. It is difficult to see why manifestations of a process of such early origin should so frequently be de layed till well on in post natal life. End arteritis as an alternative cause of vascular insufficiency has not been a consistent feature of pathology reports while it has often been noted in infants with no sign of the disease. In any case even syphilitic hyperostosis is now believed to be due to toxaemia rather than endarteritis

The serological responses to a wide range of bacterial infections were investigated, with negative results by Shuman [30], who also reported unproductive investiga tion by Foley into staphylococcus aureus calcium utilisation. In so far as the strepto coccus is related to the collagen group of diseases it deserves attention for possible connection with a disease which appears primarily to effect the myo-periosteum especially since the onset of symptoms has often been preceded by upper respiratory

tract infection or conjunctivitis [1 18 31 30 39 present case] The streptococcus has never been cultured, however and Sakula [36] found the antistreptolysin titre to be low in his case.

Virus infection might well cross the placental barrier Of the known virus af fections of bone vaccinia osteitis causes strikingly similar lesions of the diaphyses. As in many other cases, vaccinia is exonerated in this present instance for neither mother nor child had been vaccinated Thiersch s work in 1948 [46] on transmissible avian osteopetrosis showed that condition to have superficial similarities to infantile cortical hyperostosis, including predilection for the shafts of long bones and the sparing of digits, but in its natural progression to a state more like Engelman s disease these similarities fade Virus studies, directly on tissue and indirectly on serum, have been uniformly negative [6 12 13].

Published reports of congenital toxoplasmosis mention no bone pathology [2, *Lancet editorial* 14/1/61]) In our case findings were against it

There is no evidence of exogenous intoxication. The skeletal lesions of fluorinosis, in regions of high soil and water content are quite different in respect of age group affected, clinical appearance and distribution [4.] As for endogenous intoxication, toxaemia of pregnancy has *only occasionally* and probably fortuitously been associated.

Racely *et al* [34] reported a case associated with familial allergic diathesis, and Morrison s case [31] presented as allergy to soybean milk formula. These cases apart, there is no other published suggestion that allergy might be implicated.

Oestrogenic hormones are capable of producing diaphyseal hyperostosis in lower animals. Schlumberger [37] *noted this* during the *ovulating phase in female parakeets and reproduced these features by administering Stilboestrol. The phenomenon is known to occur in mice given* oestrogens [40] but here the bone change and its progression are rather dissimilar Oestrogens are rendered non-oestrogenic by the liver but the nature and metabolic effect of the residual non-oestrogenic substance are unknown [53] In the present case no oestrogenic steroid was administered within ten years of pregnancy Bennett & Nelson [4] considered that massive oestrogen therapy given to their patient prior to pregnancy may have been aetiologically significant, but theirs is the sole reference to the possibility of exogenous oestrogen effect It is, of course possible that transmission of maternal oestrogen to a susceptible child may directly (or indirectly through consequent metabolic disturbance) be responsible for the changes. Steroid excretion patterns which are being established for the newborn, might be applied informatively

From their failure to find any possible cases in a search back over twenty years of filed films Sherman & Hellyer [38] inferred that this might be a new disease The paucity of earlier reports, however may have been due to the too ready acceptance of such changes as luetic, prior to the dethronement of syphilis as the repository *of the otherwise inexplicable*

Pathology

The pathology is not characteristic of any *particular form of affection*—it excludes

neither viral hormonal nor vascular bases of explanation. The essential feature at the stage of soft tissue swelling is marked thickening of the periosteum which is packed with fibroblasts Round the earliest masses of new bone there is prominent oedema and vascularity Here and there are foreign body" giant-cell systems and focal aggregations of polymorphonuclear leucocytes. There is no sign of necrosis

Later the oedema assumes a mucus-like character extending out into related soft tissue where small areas of degeneration necrosis, and fibrosis may be found [1_]. The bone marrow may be slightly fibrotic without abnormal cells [1* 38 44] Haemorrhage is not a feature and cellular infiltration variably present is never marked [20 44].

As the new-bone formation reaches its peak, a mesh of fibrous strands is found passing out from the still oedematous and thickened periosteum, through muscle to fascia and even subcutaneous fat, though skin remains unaffected. Muscle is invaded by new bone and contains area of necrosis and atrophy Only Sherman & Hellyer [38] draw attention to intimal proliferation in blood vessels. This was not present in our wn case

Mossberger case [3], which died at an early stage showed, apart from recognised stigmata of the disease a generalised, lymphoid hyperplasia Lymph node enlargement is however exceptional and where enlarged nodes ha e been biopsied they ha shown no specific changes [33 44]

Ther is no interference with skeletal growth Onl O Reilly [33] remarks that the bones re left larger and radiologically older than would be expected from the chronological age

Treatment

Pain and fever do not require special attention. The anaemia responds to iron though blood transfusion may hav to be considered.

In a disease so variable in severity and duration, and inconsistent in remission and exacerbation, it is difficult to assess the value of empirical treatment such as steroid therapy Bush & Merrell [7] were the first to report on this aspect using corticotrophin (10 mg six-hourly decreasing to 5 mg daily for maintenance) with eosinophil control Both they and Sweeney [45] who used prednisone found apparent improvement based on demeanour temperature and ESR changes. Caffey (quoted by Gellis [_5]) takes a strong stand, insisting that employment of steroid therapy is obligatory in all cases Even his authoritative viewpoint has failed to gain general acceptance and many feel that a disease which in the majority of instances is fairly mild, does not demand the risks of such therapy Most would prefer to hold steroids in reserve for their possible value in the severe case

Summary

The evolution of knowledge concerning infantile cortical hyperostosis to the stage of a well-defined disease entity is outlined nd a typical new case presented in hich the outcome wa t tal resol tion in just over a yea

The l terature reviewed in an ttempt to present the present stat f kno ledge concerning aetiology pathology nd treatment nd the lines long hich further

enquiry might be channelled. There is an implicit plea for increased awareness of the condition by all doctors concerned in the management of infants.

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18, Beechgrove Drive
Belfast 6
Northern Ireland

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Arne Dahlqvist Hereditary Disaccharide *Intolerance*

A new group of diseases in children, hereditary disaccharide intolerance has been described in the literature during the last few years. They seem to be caused by absence of one of the intestinal disaccharidases with resulting intolerance for the corresponding disaccharide Usually only a single enzyme is missing The specificity of intestinal disaccharidases is rather complicated (Table 1) Some of the enzymes hydrolyze more than one substrate On the other hand, one of the substrates, maltose hydrolyzed by several enzymes. *Of the digestive defects which are* of clinical importance only *isomaltose sucrose* and *lactose* intolerance can be caused by the absence of single intestinal disaccharidases *Maltose* intolerance which can also give symptoms, requires the simultaneous absence of several enzymes, and is probably always accompanied by intolerance for isomaltose and sucrose The cases of disaccharide intolerance described in the literature seem to conform this conception. Isolated *lactose* intolerance has been described in twelve cases, and isolated *sucrose* intolerance in seven cases. Only one instance of *maltose* intolerance has been described, and as expected from the specificity of the intestinal disaccharidases, this patient was also intolerant for sucrose Isomaltose had not been tested. No case of isomaltose intolerance has been described, partly because *isomaltose* is not available commercially By tolerance studies with an enzymically prepared mixture of isomaltose and isomalto-oligosaccharides, the existence of isomaltose intolerance with clinical symptoms has recently been revealed. The relationship of this type of disaccharide intolerance to other types is at present under study

DISCUSSION

B Vahlquist The new observations concerning sickness conditions depending on specific enzyme deficiency in childhood have understandably aroused great interest among pediatricians I wish to congratulate the speaker on his fine presentation. I should like to ask two questions: *Should one expect* to find the condition also with partial enzyme defects, which however produce clinical symptoms? What is the present view concerning the activity of starch splitting enzymes during the early neonatal period?

Arne Dahlqvist (1) It is true that there is lower amylase activity in small children than in adults. Amylase is a very active enzyme We have measured amylase activity in adults during digestion of a starch meal and found that intestinal amylase could hydrolyze the starch completely to di and monosaccharides in 1 or 2 minutes while the intestine required 1– hours to absorb the sugar (Dahlqvist & Borgström Biochem J 81 411 1961) A decrease in amylase activity of 10–20 times can probably occur before starch digestion is disturbed — ( ) Partial forms of disaccharidase deficiency may well occur In fact we do not know whether the described case lacks the enzyme entirely or has inadequate enzyme ac-

TABLE 1 *Disaccharidases in homogenates of human small intestinal mucosa*

Enzyme	Substrat	The relative importance of the enzyme for hydrolysis of each substrate. (Total activity set at 100)
Isomaltase – Maltase I	isomaltose	100
	maltose	50
Sucrase – Maltase Ib	sucrose	100
	maltose	25
Maltase II	maltose	15
Maltase III	maltose	10
Trehalase	trehalose	100
Lactase – Cellobiase	lactose	100
	cellobiose	100

tivity as an enzyme analysis was not done. Anal sis of the intestinal content for disaccharidase activity i not worthwhile since this enzyme is present within the mucosal cells. Enzyme analyses can therefore only be done by mucosal biopsy. A series of such examinations on disaccharide intolerant pa tient is planned for this coming spring. — (Reply Professor Lindqvist) 1 The di saccharides are partly broken down by bacteria in the large intestine which is shown by the faeces low pH and high level of low molecular organic acids. How high a percentage of the administered dose of disaccharides is excreted in the faeces is not known. In cases of saccharose intolerance the fecal saccharose concentration on half dry weight has been measured, but all investigators have neglected t measure the total faeces. — 2 A lack of activ absorption of glucose may result from hemical defect. As far as I know such case has not been described but i ould be expected that the patient would ha serious symptoms. — 3 Salivary amy lase probabl pla ery small role in amy lase activit in the intestine. In adult ith pancreatic disease w ha found low amylase activity in the small intestine. It is possible tha the f ndings might be somewhat different in children.

A. Gyllenswärd and G. Holmgren: Hearing Tests at Child Welfare Centers

The Child Welfare Centers hav been able t enlarge their scope because of improved social-hygienic conditions. There has been much interest in routine testing of hearing before school age. A simple and reliable method has been available prior t a few years ago when Barr described the play audiometer. Using a modified technique the authors ha ttempted t study the feasibility for testing hearing of 4 year old at Child Welfare Center. They also wished t learn whether a more general introduction of such an examination was indicated. The study has so far included 1 0 4-year-olds in Boden and 295 in Kiruna. These areas were chosen in order to evaluat the factor of availability of an ea specialist. There is an ENT department at Boden Hospital, but patients in Kiruna must tra el considerable distance t be seen by an ear specialist. Hearing tests on small children were done by a trained udiometrist a method hich was repeatedly found t be acceptable. Almost 10 of children had hearing defects. Of these 1 2 were mild and transient and did not req ire special treatment. The majority of the rest which were relat vely more com-

mon in Kiruna than in Boden, were amenable t therapy and resulted in normal hearing afterwards. Three cases of more serious hearing defects were discovered in both areas. One patient required a hearing-aid and the others special hearing and speech training or operation It is the authors opinion after this preliminary study that testing of this type is of value. In some cases, hearing damage is prevented, and in others adequate therapy can start at an earlier date than would otherwise be possible Even though the results are not so striking quantitatively they are of great significance for the particular individual.

DISCUSSION

J Ström I have listened with great interest t Åke Gyllensward's presentation regarding hearing tests in small children. For several years, I have tried to interest our ENT specialists in developing a practical screening method for discovering hearing damage. Such a method is available for eye examinations. Joachimsson and Nordlow in Vanersborg have led the way and the latter's method for sight testing is being used in several areas. Arranging hearing tests, however has met with greater difficulties. The study from Boden and Kiruna shows that these can be resolved with the help of B Barr s play-audiometer Carrying out these tests, however is a different problem from sight tests. Nurses can conduct the latter but hearing test must be done by an audiometrist The value of such tests should be evident from Gyllensward and Holmgren s data.

G. Brante K. Kaijser and P A Öckerman
Glycogenosis in Four Siblings

In 1952 Gerty and C. F Cori described the absence of liver glucose-6-phosphatase activity in one type of glycogenosis. Rapid development of methods for determination of enzymes in the metabolism of glycogen has since made possible the classification of hereditary glycogen storage diseases into seven different types. Four siblings with glycogenosis have been studied by the authors. Diagnosis of the exact type in two of the children was btained by enzyme determinations of liver and muscle biopsy specimens done by Prof H Hers, Louvain. A total lack of activity of glucose-6-phosphatase in the liver wa revealed, whereas the activity of amylo-glucosidease and phosphorylase were normal in both liver and muscle. There was a moderate increase of glycogen content in liver but not in muscle. The clinical and laboratory picture is the same in all four cases including significant hepatomegaly In the two cases investigated histochemically the cause of the latter was obviously an increase in the size of the liver cells from glycogen and fat accumulation without cirrhosis. Symptoms are infrequent apart from slight epigastric pain and nose-bleedings. The eldest of the siblings is now 16 years old. Hypoglycemia is absent or insignificant. Only very slight decrease in fasting blood glucose values has been noted occasionally Serum cholesterol and total fat are normal or slightly increased. Serum GOT and GPT as well as ESR and electrophoretic α_2 and globulin fractions are consistently elevated, but liver function tests are normal. Increase in bleeding time and serum uric acid are also found Glucose tolerance tests are normal. Epinephrine and galactose tolerance tests show no increase in glucose levels although serum lactate is increased in the latter test. The biochemical background of different types of glycogenosis is discussed as well as the reasons for the metabolic changes observed. Finally an outline is presented which tries to classify the cases of glycogenosis described in Scandinavia. It is concluded that ours are the first proven cases in Scandinavia of the glycogenosis type due to lack of glucose-6-phosphatase.

DISCUSSION

Arne Dahlqvist The present concept of glycogen metabolism has facilitated understanding of the role played by quantitative

changes in enzyme activity in the etiology of glycogenosis. Absence of diminished activity of one or another of the enzymes have been discussed as causes of glycogenosis. Is it not possible that this also occurs as a result of the increased synthesis? The activity of the synthetic enzyme UDPG-pyrophosphorylase and UDPG-glycogen transferase should probably be investigated in cases of glycogenosis.

Gunilla Berglund Treatment of Idiopathic Thrombocytopenic Purpura by Plasma Transfusions. (Will be published in Acta Pædiat (Stockh) 196.)

Lill an Gottfarb, R. Lagercrantz and A. Lagerdahl Cooperation between the Psychologist, Physician and Nurse in Child Welfare Centers

The Child Welfare Centers can make important contributions t the child mental health and adjustment. Mothers often need help and advice. The so-called behavior disturbances—excessive thumb-sucking, bed-wetting appet te and sleep disturbances, pronounced anxiety and restlessness, temper tantrum et are very common. They can be symptoms of maladjustment. Often they upset the parent and not infrequently worsen their attitude towards the child upbringing. In Stockholm Child Welfare Centers during the last years, child psychologists have been employed from the department of child mental health. The child psychologist have stimulated doctor and nurses interest in the field of mental hygiene Short courses and informal discussion groups have been arranged with child psychiatrists. The physicians and nurses interview with the mother has become more concentrated in this field. The psychologist has assisted in both finding and advising the mothers who needed help and in deciding which cases should be referred to the child psychiatrist. Those mothers who could be assisted in the Welfare Centers were permitted more frequent office sessions (financial support for this was provided by the Medical Board) and home visits. Talks with the psychologist gave mothers an opportunity to discuss their problems. About 10% of the mothers seen in the Welfare Center have required extra assistance and above one percent were referred for child psychiatric help The psychologist has also taken part in discussion groups for mothers of children of a given age and for mothers with similar problems, as for example sleep disturbances. The psychologist has also assisted in the registration of behaviour disorders and research projects.

DISCUSSION

J Ström. I am glad that Lagercrantz has taken up the question of mental hygiene in our Child Welfare Centers. Despit many years effort to stimulate interest through the Medical Board and through the child welfare delegation of the Swedish Association for Social Welfare (by means of many conferences for different personnel groups within the counties and Welfare Centers) the response has been luke-warm. I feel that this is question of major importance for the future development of the Child Welfare Centers One often hears pediatricians say that this is a problem for child psychiatrists. I feel that this is incorrect. The common problems of development the simpler behavior disturbances as well as the milder neurolabile symptoms of children should be dealt with by pediatricians and practitioners in lose cooperation with nurses Much can be gained, as Lagercrantz has shown by the help of a psychologist who stimulated and instructed group discussion. There are great and interesting possibilities here which should be noted. Naturally cooperation with child psychiatrists should be established nd the more difficult cases requiring analyses should be referred for psychiatric care One find in Lagercrantz interest ng analyses that no less than 10% required special medical-psychological help I 90 of these cases this alone has been enough and only 10 % required referring for psychiatric examination This gives a lear picture of this hole question.

Fritz Karlström. We have stated previously that mental care in Child Welfare Centers should be managed by the pediatrician and not by the child psychiatrist. Obviously local conditions must be taken into account and used to best advantage. In Karlstad a doctor from the children's psychiatry ward with experience in pediatrics gives consultations twice a month to children with milder mental problems. Children are referred by the Children Welfare Centers. Two to four mothers with children are seen every hour and this arrangement seems satisfactory. In reference to Professor Lind's announcement that mothers are given instruction in child mental care we thought to go still further. We have considered teaching future mothers the elements of mental child care at the same time as they receive instruction in care of the newborn. Mental care seems of equal importance as care of the body. A grant has been received from the county council and we hope to begin this program shortly.

B. Hellström, F. Lindsell and B. Wengl. On the Excretion of Tryptophan Metabolites in the Urine in Infancy. (Will be published in Acta Pædiat (Stockh) 196_.)

S. Sjöl..., G. Wallenius and L. Wran. Haemoglobin Bart's and H in an infant boy.

A newborn, full term boy was followed until the age of four months. At birth he appeared extremely ill with generalized oedema, ascites, enlargement of the heart, liver and spleen, petechial haemorrhages, and cyanosis. Other abnormalities included undescended testes, hypoplastic scrotum, abundant skin folds at the back of the neck, and dysplasia of the external ears. Laboratory investigation revealed a normal haemoglobin concentration, reticulocytosis, and thrombocytopenia. Coombs's direct test was negative. After incubation with brilliant cresyl blue numerous erythrocytes showed coccoid inclusion bodies. At the age of twelve days, haemoglobin electrophoresis on starch slab at pH 8.6 disclosed a fast-moving abnormal component constituting about 20% of the total amount. The migration rate and ultra violet spectrum corresponded to those of haemoglobin Bart's. The general state of the infant improved without treatment. The thrombocyte count became normal. The reticulocytosis disappeared after a week, but reappeared after another ... months, 5-10% of the red cells being reticulocytes. At this time, the haemoglobin content and haemoglobin concentration of the erythrocytes were found to be very low (MCH 19 $\mu\mu g$, MCHC ...4%). Haemoglobin electrophoresis was repeated several times during the first 4 months of life. At 2½ months, the relative concentration of haemoglobin Bart's had fallen a little, the number of red cells with inclusion bodies had increased, and a new electrophoretic component with still higher anodic mobility was observed. The solubility of the fastest moving component, its migration rate, its ultra violet spectrum, and the parallelism between its concentration and the proportion of red cells with inclusion bodies indicated that the component was identical with haemoglobin H. The relative concentrations of haemoglobin H and Bart's at ... months were about 10% each. The child's parents were studied by routine haematological methods and by haemoglobin electrophoresis. No abnormalities could be found. The content of haemoglobin A_2 and F were normal. The pedigree has been traced back for at least three generations, and the boy appears to be of 'pure' Swedish descent. Dr Phaedon Fessas of Athens has kindly investigated and corroborated the identity of the abnormal haemoglobins.

Bengt Hagberg, Patrick Sourander and Lars Therén. The Clinical Importance of Peripheral Nerve Changes in the Diagnosis of Leucodystrophy. (Will be published in Acta Pædiat (Stockh) Suppl. 135, 196_.)

DISCUSSION

B. Lindquist. Biopsy and microscopic examination of N. suralis in cases of metachro-

matic leucodystrophy is clearly a valuable supplement t other investigations—such as examining the chromatic sediment and sul phatides. In which stage of the disease are these method most likely to be positive? —

B Hagberg Sural nerves biopsies have only been examined in the advanced stage of the disease The clinical picture of met chromatic leucodystrophy is characterized by weak deep reflexes, muscular weakness, with resultant valgus deformity of the leg and foot associated with root pains. These findings suggest early involvement of the second neuron. The test for metachromatic sediment in the course is non-specific and should only be used as a simple screening method. A brown metachromatic substance is normally found in infancy nd is present in a number of conditions in older patients During the latent phase of metachromatic leucodystrophy the test is not necessarily positiv Repeated tests are therefore necessary Nor is the demonstration of an in creased quantit of sulphatides in the urine in itself evidence of the disease Only in combination w th a quite distinct paper chromatography pattern (Hagberg and Svennerholm, *Acta Paediat* (Stockh), 49 690, 1960) does the sulphatid increase ppear to be pathognomonic for metachromatic leucod strophy These hanges seem t occur very earl probabl even before the disease is manifest linically

Yngve Larsson The Organizati nd Functions of Clinic for Juv nile Diabetes

In iew of the poor long-term results of j venile diabetes mellitus, more intensive met bolic control is considered the thera peutic lterna re hich has to be gi en serious long term trial. The consequences of this opinion regards the organization of the diabetic clinic are described. The need he management of juvenile diabetes for he sub-specialities represented n the pe dia ric univ ersit clinic emphasized. The role of he diet tian and the principles of dietary trea ment are outlined Teach ng of he pa ien regarded as one of the main therapeutic tools and methods used for this purpose are described. Patients with juvenile diabetes should remain under pediatric su pervision until they ha reached complete maturity

Göran Sterky Consumption of Calories and Nutrients among Diabetic and Nondiabetic School Children. (Will be published in Acta Paediat (Stockh) 196)

DISCUSSION

Bo Vahlquist It was very interesting to learn of Sterky investigations. It would be a good thing if representative sections of the population in different parts of the country had their cost consumption outlined in a similar way As regard the idea of recommended daily allowances the Americans consider this figure very generous. It would be better if the given values were several times larger than the minimum requirement

M Fraccaro J Lindsten and M Polani Hermaphroditismus "Verus" w th XO/XY Mosaicism

A genital anomal with phallus and bifid scrotum as noted in a newborn. In the left inguinal region gonad was palpable N other malformations could be demonstrated. Sex-chromatin studies on skin biopsy buccal and blood smears and cells grown vitro showed negative pattern. X-ray examination of internal genit lia nd laparotomy revealed vagina, uterus nd fallopian t bes of ordinary size and shape The righ gonad as of the type small seen in Turner syndrome in the female A he end of the left be there estis like gonad and next t th an other smaller structure I the lef inguinal region here ale hernial sac Histologicall he righ gonad as f ery low differentia ion The testes in the left side had more leveloped testicular and epid d mal structures Chromosome st lies of cell from the rial gonad sk n nd bone

marrow revealed a typical XO karyotype with 45 chromosomes. Mosaicism with 45 XO/46 X"y karyotypes were found in cells from peripheral blood. The Y-chromosome however was smaller than usual, probably due to a deletion. A translocation could not be excluded. Both parents had normal karyotypes. At the age of years the child reared as a girl, had developed normally So far chromosomal studies have been reported in 13 cases of true hermaphroditism. Eight cases had an apparently normal female karyotype with positive sex-chromatin. Five had a mosaicism with 45 XO/46 XY and negative sex-chromatin Two out of these 5 cases with mosaicism had an abnormal Y chromosome probably due to a deletion. The effect of such an abnormal Y-chromosome upon the sex determination mechanism is not clear Up to now testicular structures have been found in all cases with a deletion of the Y-chromosome The genes which act upon the development of the testis thus seem to be located near the centromere

Meeting Dec 2 1961
with Swedish Society for Obstetrics and Gynaecology and Swedish Society for Anaesthesiology

Panel discussion. Resuscitation of the New-born Chairman. J Lind Members of the panel. J Asplund O Colander L. Engström, M. H.son Holmdahl, P Karlberg, G Rooth, B Westin, P E. Wiklund and R Zetterström.

Meeting Jan 12, 1962

J Lindahl and Å Espmark Smallpox Vaccination in Patients with Exzema

J Ström Coxsackie B_5 Infection in Two Siblings

Coxsackie B infection, type 5, in two sisters, 5 and 14 years of age is reported. The younger had serous meningitis and—an unusual finding—a maculous exanthema, which has previously been observed only in certain Coxsackie A infections. The elder sister had myalgic symptoms and pericarditis followed by myocarditis. Viral and serological tests proved the presence of the infection Earlier observations, similar to the last case, suggest that infection particularly with Coxsackie B type 5, is likely to be accompanied by pericarditis.

L. Kjellén and G Sterner Incidence of Adenovirus in a Children's Hospital (One Year Study)

During the period March 14, 1959–March 13 1960, 2,405 children were admitted to Flensburgska Children Hospital in Malmö From 1 923 of these, faeces were obtained for a study of the incidence of adenovirus on admission. These studies were performed in the virological department of the Bacteriological Institution in Malmö General Hospital. Only HeLa cells were used for cultures. Clinical classification of the total material showed that 1 093 children on admission had signs of an acute respiratory infection while 818 suffered from non-contagious complaints. About 80% of these children were included in the study In the former group, 5.3% of the cases excreted adenovirus, as against only 0 6% in the latter (control group) Most of the total of 70 (strains) of adenovirus belonged to types 1 2 and 5, while only a few belonged to types 4 6 and 7 Adenovirus type 1 2 and 5 were isolated from children 3 months to 3 years old, half of whom were less than 1 year old. Adenovirus excretion occurred during all months of the year except March, 1960. The lowest frequency was recorded in August and September 1959 Probable nosocomial infections with adenovirus type 1 2 and 5 were found in 11 of 295 children, whose faeces were examined not only on admission but also later during

their hospital stay Most children who excreted enterovirus 12 (strains) belonging to poliovirus, and 40 (strains) belonging to Coxsackie virus also had signs of acute respiratory infections on admission.

Symposium on New Penicillins

Gösta Wallmark New Penicillins, Survey

The discovery of a method to produce the penicillin nucleus, 6-amino-penicillanic acid, has made possible the development of a large number of new penicillin variants. A few of these have demonstrated such properties that they have been made available to the clinic The new semisynthetic penicillins might be separated into three groups. The *first group* includes phenoxyethylpenicillin, phenethicillin, and phenoxypropylpenicillin. The members of this group closely resemble phenoxymethylpenicillin, penicillin V being resistant to acid and well absorbed after oral administration. With the new variants higher blood levels are obtained, but this advantage reduced by the somewhat lower activity on principally penicillin sensitive organisms. These new compounds have a moderately better effect on penicillinase producing staphylococci This does not warrant their use in infections caused by such bacteria, but it might be of value in the treatment of other infections when penicillinase producing staphylococci are present as well. The *second group* is represented by methicillin and phenylmethylisoxazolylpenicillin (P 12) which both resist penicillinase Their antibacterial activity is significantly less than the penicillins in the first group, P 12 being more active than methicillin, but this disadvantage is overcome by an increased dosage The clinical use of these two penicillins might be restricted to infections caused by penicillinase producing staphylococci. The *third group* represented by aminophenylacetamidopenicillin, penbritin This variant which is well absorbed after oral dosage has an activity on Gram-positive bacteria similar to penicillin V but it is definitely more active against a number of Gram-negative species, including E. coli and Salmonella, and can thus be characterized as a broad spectrum antibiotic.

S Espmark, P Gerdén, A Gunnar Å Ljunggren and M S[illegible] A Comparison of Phenoxyethylpenicillin and Penicillin-V Acid in the Treatment of Scarlet Fever

Two hundred and eighty-three cases of scarlet fever have been treated with penicillin—144 with phenoxyethylpenicillin (Alfacillin) and 139 with penicillin V acid (Meropenin) The two series have been compared as to duration of fever disappearance and reappearance of hemolytic streptococci, changes in ESR and antistreptolysin titre and in complications. No differences were found in the duration of fever increase of ESR, rapidity of disappearance of streptococci, reappearance of streptococci during or after treatment A tendency to higher antistreptolysin titer among those treated with phenoxyethylpenicillin may show a trend but the difference is not significant A significantly greater incidence of complications (impetigo lymphadenopathy and erythrocyturia) was found in the group treated with phenoxyethylpenicillin. A follow up study after treatment indicated no differences in long term prognosis.

G B[illegible] S O Liljedahl A Wickman and K W[illegible]ge Methicillin Treatment of Staphylococcus Infections in Surgical Cases

Methicillin, a half-synthetic penicillin, highly resistant to penicillinase was administered to 14 patients on the surgical service t Karolinska Sjukhuset All patients had serious infections with penicillin resistant that is, penicillinase-forming staphylococci. Six of the patients developed infection at the time of cardiac surgery All of them had clinical evidence of sepsis in six positive blood cultures were obtained Three of these patients died, one of them as a result of a non-infectious complication. Six patients

had extensive burns with secondary staphylococcal infection. Staphylococci were isolated from the blood in three cases. Of the other two one had septic arthritis with staphylococci cultured from both the joint and blood. The other patient was operated on for a bladder tumour and developed a wound infection. Methicillin was administered to these patient in a dose of 1 g 6 intramuscularly or 6 g/day intravenously. The blood level was determined in 9 patients and found to be satisfactory. Duration of treatment varied between 7 days and 9 weeks. The primary result of treatment was good in all cases, both clinically and bacteriologically. Negative cultures were obtained generally after 5–6 days treatment. The later result was less encouraging as staphylococcus infection recurred n nearly all cases. To counteract this tendency it was proposed that long term or intermittent treatment be tried. Infection with gram-negative bacilli was a frequent complicat on. Broad spectrum antibiotics were recommended for clinically serious nfection of this type. In conclusion, methicillin should be reserved for treatment of serious infections with penicillin-resistant staphylococci. In spit of the risk of recurrence, it ha proved valuable in improving the patient condition sufficiently to permit other measures to be carried out as for example the application of skin grafts to burn injuries. By this means definite improvement can be obtained.

St g Wahlqvist New Penicillins. Research Fronts

The isolation of 6-amino-penicillinic acid (6APA) and its production on a large scale have made possible the commercial preparation of various semi-synthetic penicillins. The chemist' ability to vary the structure of the side chain to the basic molecule is considerable, but systematic biological test ing is generally limited to discovering whether the combinations fulfil the requirements: (1) Superiority t penicillin V — (2) Resistance to penicillinase and (3) Activity against gram negative bacteria. Various new penicillin derivatives are now available which satisfy one or more of these requirements. Their properties and effectiveness in treatment of various infections are discussed. Investigation of bacterial enzyme production, the significance of protein-binding for chemo-therapeutical effect and other research problems are outlined in relation t the development of new penicillins with optimal effect on different infections.

Meeting Jan 31 1962
with Swedish Society for Endocrinology and Swedish Society for Gynaecology and Obstetrics

A Jost Paris: Sex Differentiation f the Foetus and the Use of Steroids during Pregnancy

Meeting Feb 9 1962

A Bergstrand, C. G Bergst d N Engström and K. M Herrl n. Renal Changes during Treatment with Oxazolidine-Diones

A nephrotic syndrome is a rare complication in children to treatment of epilepsy with oxazolidine-diones. Experimental investigations also indicat that trimethadione in large doses may have a nephrotoxic effect In order to find out if slight and linically not observable damage to the kidneys may occur during treatment with these drugs, we have investigated seven cases aged 14 1 2 16 1 2 years which have been treated with oxazolidine-diones for very long periods. Repeated examination of the urine showed only slight and transient haematuria or proteinuria f three of them and all of them had normal

urinary findings at the time of the investiga tion. Light microscopy of renal needle biopsy material showed no glomerular or tubular lesions. Electron microscopy of the glomeruli showed wide variations in the p- pearance of the capillary epithelial cells. These are regarded as physiological varia tions and not as pathological phenomena. The investigation has not shown any signs of renal damage which could be scribed to the treatment

K. Ekengren and K M Herrlin The Ske letal Asymmetry f Spastic Infantile Hemi plegia

The length of the long bones of the upper and lower extremities wa radiographically measured in 58 children and adolescents aged 2½–20 years (33 boys and 25 girls) with cerebral palsy Thirty-nine had right-sided hemiplegia and 19 left-sided. The humerus and radius were shorter on the paretic side in 43 and 37 patients respectively The retar dation of growth both for the humerus and radius w at most 10 of the length of the bones on the non-paretic side the range in absolut figures was 1 20 mm (M ~ 11 mm). In the rest of the cases humerus nd radius were of equal length on both sides. The femur was shorter on the paretic side in 33 patient (max ..5 .. range 1–6 mm; M 4 mm) and longer on the paretic side in 19 (ma 3 5 .. range 1 14 mm; M 4.5 mm) The tibia shorter the paretic side in 49 patient (max 7 .. range 1 23 mm; M 9 mm) and longer on the paretic side n 8 (max. 1 .. range 1 4 mm; M 1.5 mm) In the rest of the cases the femur and tibia were of equal length The investigation included also oentgenographic studies of the skull, hands nd feet It is intended to enlarge this series nd to compare the findings with clinical dat

(lle an Enk and) gt Larsson Glucose Tolerance Tests in Children. \ M thodolog ical Stud

Glucose olerance was studied in 46 chil dren, ged 2 15 14 cases of glycosuria of unknown origin, 5 cases of obesity and 27 controls. Methods: Oral standard glucose tolerance test (OTT), intravenous GTT and oral prednisolone GTT the latter modified from F jans & Conn. Capillary blood sugar was determined according to the true glucose method of Ek & Hultman In the intra e nous tests the disappearance rat of glucose (k_G) wa 1 73 ± 0.20 in the glycosuria cases and 1 63 ± 0 08 in the control group This difference wa not significant, but the range was larger in the former group In the pred nisolone GTTs, a significantly higher blood sugar level was obtained than in the standard GTTs in the glycosuria groups as well as among the controls, and no difference was observed between the means of the t o groups In single cases, however the curves were highly abnormal, making prediabetes strongly suspected. In obesity low k_G-values were observed, and the blood sugar level in prednisolone GTT w significantl higher than in non-obese cases These findings may support the theory of metabolic relation between prediabetes and obesity Thus, in tra enou GTT and prednisolone GTT gave in many cases diagnostic information unobtainable by the standard test.

T Müller The V lue of Anastomotic Opera tion in Congenital Heart Disease

Anastomoses bet een the pulmonary ar tery and aorta in cases of cyanotic congenital heart disease as devised by Blalock and Taussig in 1945 The opera ion though palliative was designed to increase the pul monary circula ion n cases of Fallot tetralogy tricuspid tresia nd other anoma lies with decreased pu lmonary flow orde to raise the arterial ox gen level he systemic rcula ion Satisfactory surgical res l ha been reported by Taussig and P tt America, Campbell Br Don zelot France Derra erman M heimer n eden nd hers During the la er part of the 19 .. method ere evol ed for otal corre ion of in rac rdiac defec employ g heart l g machine was dev loped Thus new ec ique es

perior to anastomosis as it aims at correcting the underlying anomaly. The anastomotic procedure can still be used for patients with Fallot tetralogy who are young or so seriously ill that they cannot be expected to reach a suitable age for total correction. Cases with complicated defects or with under-development of a cardiac chamber or vessel may sometimes require an anastomosis by reason of the greater risk attendant on total correction. Cases of tricuspid atresia with decreased pulmonary flow should have an anastomosis operation performed on the left. An anastomosis operation does not exclud the possibility of subsequent total correction. The results of an anastomosis on 161 patients with congenital heart disease is reported. The operative mortality was 12.7%. The observation period for the survivors was between 4 months and 10 years 10 months. During the control period, 9 patients died, mainly as a result of cerebral and pulmonary complications. Among the survivors, the operative result was excellent in 53%, marked improvement in a further 40%, while 7% remained unimproved.

P. O. Hillborg: Th Heredity of Gaucher Disease in Sweden

The author has tried t collect all cases of Gaucher disease in Sweden by sending an inquiry to all paediatric clinics, haematologist and pathologists in the country. Thirty-six cases recorded during the last 36 years were found in this way. Nineteen cases were located in a northern region of the Norrbotten–Vasterbotten counties and 17 in a southern region of south west Sweden. As 10 of the cases in Norrbotten county occurred in 6 families known to be partly related, the parish records were then examined. Of 1 parents, 7 were descendant of one man, born in about 1630 in the community of Överkalix in the Norrbotten county; while 7 were descendants of another man with the same name, place and time of birth. Possibly these two men are one and the same. The pedigree shows clearly that the type of inheritance is autosomal and recessive. Of the 10 cases in these 6 families, 8 were born in Överkalix during the years 1934–51. The whole number of live births for the same period was 5150, so the frequency of the disease in Överkalix was 1:644 or 16 10,000. This frequency is very high and the explanation for this is that the community of Överkalix has long been geographically and culturally isolated. The histological chemical and haematological findings in the patients were quite typical of the disease. In the bone marrow of several of the parents, grandparents, brothers and sisters of the patients, the author has found cells, strikingly like the typical Gaucher-cells present in all of the patients. It is possible that we now have a method to show which of the relatives are heterozygous.

Lars Engström, Bengt Eriksson, Petter Karlberg, Ingvar Nylander, Bengt Saltin, Clees Thorén and Per-Olof Åstrand. Hard Swimming Training f Girls 12 16 Years Old—the Medical View-point

Thirty girls aged 12–16 who took part in hard swimming training for periods of 6 months to 5 years were examined as to physical and psychic development and health. They were of normal height and weight but 50% were relatively tall for their age. None of the girls seemed to have suffered any injury to her health. Some minor tension observed in a few of the girl could not be ascribed simply to swimming. Gynaecological examination showed pathogenic bacteria in the vagina in more than one-third of the cases, nd therefore swim training and racing must be considered undesirable during menstruation. Half of the girls said that they swam worse during menstruation, and one-third suffered discomfort in the lower abdomen. The lung heart and blood volumes a well as total haemoglobin in some of the girls, especially the lder ones, showed a high value in relation to body size but in relation to maximal oxygen uptake good functional agreement was present. This functional development can constitut an accelerated normal deve-

lopment, entailed by constitution, and/or a result of long hard training. However par ticularly among some of the older girls, the functional adaptation was so great as to exceed the expected termination of a girl normal development. These girls maximal physical performance power was shown to be either equal or bove that of the best women ski-runners in the 20--3 years old range. The highest value as regards maximum oxygen uptake was 3.75 l min on the bicy le-ergometer and 3.81 l/min while swimming. Maximal working pulse rate was normal for age and varied between 180 and 214 beats per minute The measurement of oxygen uptake pulse rate and lactic acid in the blood during and after competitive swimming was carried out and show that the pulmonary and circulatory requirements while swimming races are very considerable and make swimming a sport that demands top physical condition Even though these girls, who in many respects constitute an elit group, had good health and development, and several of them extremely good functional capacity the examination of this cross-section cannot provide the basis for any general conclusion regarding hard swim training during childhood and youth. This would require continued examinations of these girls, as well as of girls not up to elite class, but who nevertheless take part in hard training

Rutger Lagercrantz Stockholm

Norwegian Pediatric Society

Meeting March 1 1961

A. W Williamson London (By invitation) Abdominal Emergencies in th Newborn

S Eek and O Knutrud Megacolon Congenitum—a Follow Up Study

Meeting April 14 1961

B Frethem Deformities of the Thorax

Funnel chest is by far the most common anomal of the thoracic cage In this condi tion, the distance between the xiphoid process and the spinal column is bnormally short Thi anomaly may be symmetrical or asymmetrical, and becomes more marked during growth, especiall at puberty Inspir tory retraction of the sternum and displacement of the heart towards the left are common findings. In more severe cases increased trial pressure reduced stroke volume and reduced breathing capacity are often present Electrocardiographic changes not uncommonly occur as a result of displacement and rotation of the heart

Indications for surgery are:

1 Impaired cardiopulmonary function.
2 Orthopedic manifestations
3 Cosmetic disfigurement with accompanying psychological disturbances The latter indication is probably the most important, and surgical correction should take place in early childhood. In the Surgical Department B w use modification of the Sulamaa technique which is simple renders the patient ambulatory from the first post operativ da and gives a cosmeticall satisfactory result. N complications occurred in the 5 cases in hich his method was used

The second most frequent thoracic wall anomal is pigeon breast or pectus carinatum There are two main types the arcuate and he oblique form. Surgical treatment is

seldom indicated. Much rarer is the so-called Sprengel deformity characterized by failure of the scapula to descend in fetal life. This anomaly is operable.

Finally there are some very rare deformities, like defects in the bony structure of the thoracic wall of varying type and extent, and fissure of the sternum with or without ectopia cordis. These conditions may be operable.

Ragnh ld Ki l Congenital Phlebectasia

H. Sommerschild and A. Tanjum Perinatal Listeriosis

The first case of verified, perinatal listeriosis in Norway is reported. The mother was a 21 year-old seamstress from a small town near Oslo who had had no cont ct with animals. She had not been under medical supervision and the gestation period was unknown. It was her first pregnancy; the course had been uneventful and resulted in a normal spontaneous delivery. The infant was premature: weight, 2150 g; length: 46 cm. Cried immediately after birth, but was weak with reduced tonus. About 18 hours after birth a rash was observed. The general condition became steadily worse and the infant was admitted to the department at one and a half days of age. He was weak, listless, and had a skin eruption the size of a millet seed with some tiny pustules. The umbilicus was red, fontanel normal and no rigidity of the neck was present. The temperature was 39°C, respirations good, and examination of the other organs was negative. Leukocytosis with a marked shift to the left was present. Attempts at spinal puncture failed. The condition was regarded as sepsis, and chloromycetin and penicillin in large doses were given. The infant died at 2 days of age.

Autopsy. On gross examination, barely perceptible granulomas with monocytosis and Gram positive bacilli in the liver, spleen, adrenal glands, small intestine, lungs, meninges, and umbilical cord were found. There was some bleeding around the pons. There were no other positive findings.

Bacteriology. Massive pure culture of Listeria monocytogenes wa isolated from the nose. This organism was also demonstrable in samples from the throat, umbilical cord, skin pustule, blood culture, and on post mortem biopsy from a granuloma in the liver. Bacteriologic samples of the mother were taken two weeks after delivery and growth of Listeria monocytogenes occurred in a culture obtained from the vagina. The mother's serum agglutination titer was normal. Organisms isolated from both mother and infant were identical and belonged to group I Listeria monocytogenes. N growth occurred in cultures from the infant stool, nor from the mother's throat, nose or blood.

The case is regarded as typical of septic granulomatosis due to perinatal infection by Listeria monocytogenes. The clinical course, pathologic-anatomical findings and bacteriologic findings are characteristic. The infant is considered to have been infected intrauterinely and the premature birth was probably precipitated by the intrauterine infection. The mother source of infection is not known.

O. Trygstad and W. Blystad Blood Pressure Determinations in Newborn Infants with an Oscillometric Method

Meeting June 3 1961

J. Steen Johnsen Intramuscular Injections—Sciatic Nerve Injuries

For more than 40 years reports of nerve injuries following intramuscular injections in the gluteal or shoulder regions have p-peared. Extensive use of antibiotic injections in recent years has resulted in numerous reports of nerve injuries, particularly in infants. The danger of accidentally injecting drugs into or close t the sciatic nerve is considerable in a kicking infant with small buttocks. In the Pediatric Department of Vestfold County Hospital, patient received intragluteal injections of achromycin and the

urographic contrast medium "Trijodyl 25%" (8 ml in each buttock) at the age of 11 months. Unilateral paresis of the sciatic nerve with loss of function of the flexors of the knee and the muscles of the calf, as well as signs of involvement of the autonomic f bres of the nerve occurred a fortnight after the contrast injection. In the course of one year observation, the paresis has abated with physiotherapy but growth of the leg and foot has been slightly retarded. In nerve injuries following injection, both perineural cicatrization causing pressure on the nerve and intraneural cicatrization with possible axis degeneration are probably in volved in the pathogenesis. Expectant treat ment with physiotherapy and prevention of contractions is indicated. In cases where restitution does not occur, surgical inter vention with neurolysis may be tried, par ticularly if an infiltration corresponding t the nerve injury is palpable. Surgical treatment is not as rule recommended until one year after the injury Most important is preven tion. Intragluteal injections as a routine procedure in infants should be discontinued. Vessels and, more particularly nerves may be damaged. As the anterolateral part of the thigh has no large nerves or vessels, intramuscular injections in this region, mid way between hip and knee, are recommended

A Kåss: Congenital Torticollis

In Vestfold County Hospital Pediatric department 44 patients with tumor in the sternocleidomastoid muscle have been trea ted with massage and manipulations carried out by their parents, only one child out of 30 failed to regain function during a follow up period of more than 18 months. Study of the literature and our own experience indicat that congenital muscular torticollis is not rare condition. The tumor is generally detected during the first two months of lif and infants should be examined routinely for this on their first visit All infants with a palpable tumor should receive adequat con servative treatment as it is impossible to predict which patient will develop the com plet picture of torticollis. Surgery is not indicated in infancy Should operation be come necessary later on, asymmetry of the skull or face will correct itself as long as the child is still growing The operation will, however invariably be followed by some asymmetry of the neck and this may present cosmetic problem.

K. B. Keppang Differential Diagnosis in Increased Intracranial Pressure in Children

Seventeen infant with unquestionable signs of increased intracranial pressure all with papilledema were seen at Vestfold County Hospital, Tönsberg during the period 1953 t 1960 The cases were divided into three groups:

(1) Intracranial hypertension produced by neoplasm. This group included 12 cases of whom seven had supratentorial and five infratentorial tumors. Two of the former had craniopharyngiomas, fiv had gliomas. The infratentorial cases embraced three cerebellar medulloblastomas, one glioma of the pons, one bilateral acoustic neurinoma (von Recklinghausen disease). Ten patient died and the two survivors are very ill (not radically operated gliomas)

( ) Intracranial hypertension produced by pathologic processes other than neoplasm. This group comprised two cases f encephalitis and one case of intracerebral hemorrhage from a saccular aneurysm. The patients with encephalitis recovered spontaneously and the patient with intracerebral hemorrhage recovered after ligation of the aneurysm and removal of the hematoma.

(3) Two cases with benign intracranial hypertension or pseudotumor cerebri. Both patients recovered after 6 to 8 weeks. The causative factors in this condition are little known, but Davidoff (Neurology 1956–61 cases) found nine cases of otitis media and 23 cases with some infectious disease or other or history of head trauma.

Children with increased intracranial pressure require repeated clinico-neurologic examinations. Radiographic examination of the skull and EEG must be done in all cases.

In expanding lesions of the supratentorium, carotidangiography is indicated. This examination may also be valuable in expanding lesions of the infratentorium, as hydrocephalus may be detected. Examination of spinal fluid should be done when inflammation or bleeding is suspected. The indication for this examination is doubtful in suspected intracranial neoplasms, particularly in infratentorial expansive processes. In such cases, lumbar puncture is not recommended. Vertebral angiography belongs to the neurosurgical field.

G Heiberg Salem Suprapubic Cystography in Urinary Tract Disturbances in Children

The main purpose of cystography is to determine whether vesico-ureteral reflux is present since this is a pathologic finding. It is important to obtain satisfactory micturition cystograms for the diagnosis of possible bladder neck obstruction as this condition is believed to be the most common cause of vesicoureteral reflux. The technique of suprapubic cystography was described, and own experience reported. Radiographic examination of the urinary tract in children is incomplete unless it includes cystography

Meeting September 22 1961

A Njå. Report of Case

A 10-month-old boy placed in a nursery home for adoption was demonstrated. He was born at term, foot presentation. Birth weight was 3440 g, length 49.5 cm. After delivery he seemed somewhat listless with respiratory difficulty but improved rapidly His mental development has, however been retarded The infant s appearance is peculiar The eyes are markedly slanted. There is considerable mental retardation. The tongue is not enlarged Circumference of the head is 45 cm. The font nel is large, ending frontally in a 2 cm wide transverse border The ears are well formed and of normal size. Hnads and fingers are normal. The musculature is flaccid, he has difficulty in holding his head up, is unable to sit and does not attempt to stand. The boy is small, only 67 cm and the legs in particular seem short. Many of these findings seem suggestive f mongolism. The uthor is nevertheless of the considered opinion that the patient is not a mongolian idiot Chromosome determina tion was performed in April 1961 at the Human Genetic Institute. This showed 46 chromosomes with X and Y chromosomes; i.e. normal male. This finding rules out mon golism. The vast majority of mongolian idiots examined have proved to have 47 chromosomes; viz. trisomic chromosome 1. It is true that a few cases of mongolism with a normal number of chromosomes have been reported, but even in these instances the chromosome picture has not been quite nor mal in that a trebled dose of chromosome 21 has probably been present In our case the chromosome picture was very clear and typical of that found in normal males.

K. W Wefring Experience with Icterometer

An icterometer is a transparent perspex rod stained with five bands of different shades of yellow numbered from 1 to 5. The rod is pressed against the tip of the infant nose and the colour that develops following blanching is compared with the shades on the rod. The degree of icterus is expressed by the number of the shade On the basis of 147 icterometer readings correlated with parallel determinations of serum bilirubin with the Jendrassik & Grof method the following conclusions can be drawn: Icterometer is useless for evaluation of the degree of icterus in infants with rapidly changing bilirubin concentrations, as in erythroblastosis. In premature or fullterm infant with gradual development of j undice the icterometer may be helpful in deciding whether or not blood should be drawn A serum bilirubin concentration of more than 16 mg has never been found when the reading was

3 or less. Use of the icterometer in addition to clinical evaluation is more reliable than clinical evaluation alone when it comes to set the indication for serum bilirubin determination.

DISCUSSION

J. Steen. In recent years we have occasionally used the icterometer in the Pediatric Department at Ullevål Hospital. Systematic studies on the accuracy of icterometric readings as compared with serum bilirubin determinations have not been carried out, but we have the impression that the icterometer is of little value. Referring t a paper read t previous meeting we would like to stress the need for more exact serum bilirubin determinations. Hospital pediatricians should send serum t other hospitals to check their own values.

A. Smith: Infant Feeding. A Belated Contribution to the Discussion

The directions for feeding infants have changed greatly since the thirties. It was Professor Frölich great merit that he introduced simple, practical directives recommending that breast feeding be continued up to 8–9 months of age. Since then there has been a tendency t ever earlier addition of vegetables and meat, for which the main indication has been fear of alimentary anemia. In the author opinion the danger of anemia is a question that needs further elucidation. The factors that may be of importance are: daily requirement, iron concentration of milk, and iron deposits; but t decide the role of each separate factor is not possible. Parallel with this development, the ability to nurse has declined steadily in Norw y as in other countries, such as Sweden where this phenomenon has been studied by J. Ström and von Sydow. The causes for this are sundry. The author believes that the short stay on the maternity ward plays an important role and moreover that the growing use of commercially prepared baby-foods and the early addition of these disincline the mothers t nurse their babies. It is a question of whether the doctors themselves, i.e. the pediatricians, are not partly to blame for the decline in nursing ability. Conclusions: (1) The stay in the maternity ward is too short. (2) Supplemental feeding should be given after the breast. (3) Supplemental feeding should not be given too soon. (4) "Pump milk" for babies whose mothers work outside the home. (5) A more reserved attitude to commercially prepared baby foods. (6) In the critical period, at 3–4 months of age, one should try to increase the supply of breast milk by giving both breasts twice alternately t each feeding.

DISCUSSION

H. Tretteberg. I am glad Dr. Smith has again taken up the question of infant feeding. I have often asked myself how much use are our efforts, and whether mother' milk has as high a standing now as before. W are all aware that breast feeding has gone down. In Oslo Health Council annual reports there are st tistics from Sagene and Christie Street Health Stations where there has not been much change in the last years. I do not agree with Dr. Smith when he blames the falling off on the current supplemental feeding which I for one, f vor. I believe that the cause is more likely psychological. At my health station, we have approximat ly 900 infants a year of whom 500–600 are new. More than 25% have been weaned before coming, even though they are often only 2–4 weeks old. This is explained by the difficult situation the mothers find themselves in, the second week after delivery. In Oslo, all babies are born in hospitals. The mothers are admitted at the last moment, without knowing before hand to which hospital. The stay lasts 5 days t most which means that there is not enough time for instruction, and that the milk secretion has not alw ys started properly. The mothers have not sufficiently recovered and at home they suddenly must take care of everything. Nervousness dominates the situation. This spoils not only the ability t nurse but the entire mother–child relationship.

The first week home from hospital represents a big vacuum in our care of mother and child, and something must be done to remedy this defect — *M Seip* I am inclined to agree with Dr Smith that as pediatricians we should propagandise for breast feeding; but not at any cost. The ability to nurse is probably primarily psychological and it is unwise to insist too strongly on breast feeding under all circumstances. I do not think the use or non use of prepared baby foods is important. After all, we can not just dismiss the advantages of prepared foods, and we may as well face the fact that they will become more and more popular. That infants are given a more varied diet now than previously is probably first and foremost because the iron supply undoubtedly becomes too low on a pure milk diet at about 4 months of age. There are sundry other reasons too, i.e. the need for vitamin B calcium, protein, etc. Investigations now in hand at the Pediatric Department show that the need for iron in the diet from about 4–5 months of age is greater than is commonly thought. — *S Halvorsen*. That the fear of anemi mentioned by Dr Smith is well founded has been confirmed by several investigations using entirely different techniques. Investigations on hæmoglobin, serum iron (Vahlquist), and iron binding capacity of serum (Hagberg) point in this direction. In further support are studies using the isotope method (Smith *et al.*) or direct determination of iron in the bone marrow (Seip & Halvorsen) on the age at which fetal iron deposits are exhausted. All these studies indicate that the majority of fullterm infants develop iron deficiency at 5–6 months of age whether they have been fed mother milk or cow' milk, if they have not received supplementary feeding by this time. — *A Nyl*. In my capacity of responsible pediatrician in two of Osl large maternity wards I have to object sharply to the view that the hospital regime is responsible for the mothers declining bility to nurse their babies. I can assure you that those responsible for this part of the work are most eager t help the mothers make the baby t take the breast. Nor is it true that mother and child are utomatically sent home on the fifth day Discharge is frequently put off because the baby is not yet ble to suck properly However it would be an advantage if all mothers could st y in the hospital longer The vast majority of mothers nurse their babies on discharge from hospital. It is after they go home that things start t go wrong. The change from hospital life t the rush and bustle at home is no doubt a heavy strain for many and a contributory cause of the milk's disappearing — *T Strøm*. I have often reflected on the problem of natural ("nature ") infant feeding in relation to the scientific demands of today I got the answer talking t a father about breast feeding I told him that there were tribes in Africa where mothers nursed their children until they were three years old "That I have seen" he said, and I have seen mothers chew the food first and put it in the baby s mouth afterwards. "Of course," I thought there the rub I have seen that myself as a child. It happens even today in out-of-the-way places in our country so the midwives tell me. It seems to me that science has nearly completed the circle; that we are back at the diet babies have been fed from the beginning of things; i.e. breast and small portions of all sorts of food, the only difference being that today the food is artificially chewed. (This probably causes considerable loss of salivary digestion which may or may not, be of consequence.) With reference to the ability to nurse I do not believe psychological factors alone should be blamed. Still another cause is that far too many mothers are discharged from hospital on the fifth or sixth day with instructions that the infant must have so much formula in addition per day A few sensible mothers do not let this worry them and soon produce enough milk. But most take very good care to give the ordered formula and even a little extra, and this does not give the breasts much of a chance I could mention several such factors and am of the opinion that there is every reason to take up the problem once more with a view to renewed propaganda.

Meeting October 2h, 1961

O Imerslund. Impression from the Educational Hospital in Korea

O Gardborg O H I ersen and B. Torheim BCG-infection in an Infant

The patient is a girl who was BCG vaccinated t 6 weeks of age. Two days after vaccination she developed an upper respiratory infection and subsequently recurrent diarrhea. Adrenalin Pirquet was negative 6 weeks following vaccination, but the patient was not revaccinated. At the age of 5 months the patient developed a fluctuating septic fever and had leukocytosis with a shift to the left. A firm, irregular approximately orange-sized tumor was palpable in the left flank. The tuberculin reactions were negative The abdominal tumor subsided after while and was no longer demonstrable Treatment with antibiotics, antimycotics, and blood transfusions was without effect and the patient died at less than 7 months of age in shocklike condition. Examination of serum protein revealed, in one sample lacking, in another normal, and in the last greatly reduced gamma-globulin. Radiographic examination at first disclosed a tumor shadow in the pancreatic region, and later signs of shrinking process in the same area. On autopsy ascites and a thick fatty coating on the intestines and mesentery in the upper part of the abdomen were found. Swollen lymph nodes with central caseation necrosis were located anterior to the pancreas. Microscopic examination revealed specific granulation tissue with epithelioid cells and Langhans giant cells together with myriads of acid-fast rods. T bercles of this type were found in the liver spleen, lungs, adrenal glands, lymphatic nodes and in the capsules of the kidneys and pancreas. Meningitic changes were present Bacteriologic test showed that the strain of acid fast rods deviated from the ordinary human strain, but could not be differentiated from BCG strain Pathologic-anatomical diagnosis: Disseminated tuberculosis, BCG-strain.

DISCUSSION

S Dick Henriksen The enormous number of tubercle bacilli in the pus was striking and seems to indicat untrammelled reproduction. In addition to the demonstration of reduced gamma-globulin, the lack of tuberculin allergy is worth noting It makes one suspect a more general immunologic defect since children with agammaglobulinemia may develop allergy of the tuberculin type The type of colony was typical of BCG That a few guinea pigs died following the tuberculin injection was, in my opinion, due to allergic shock. There were no signs of progressive tuberculosis. One has t reckon with a general dissemination. In addition to the previously mentioned characteristics, the strain showed "cording This together with the slight resistance t PAS accords well with the BCG-strain from Bergen, while the strain from the infant father is reported to have been sensitive This constitutes additional evidence in favor of the BCG-hypothesis.

G Hall. The Influence of Neonatal Asphyxia on the Central Auditory Tracts

It has been demonstrated that children who have had asphyxia t birth often develop a loss of auditory acuity t the higher frequencies. This hearing loss is always of the same type and appears on the audiogram as a steeply falling curve t the higher frequencies. As the curve is of neurogenic type the injury must be located in the inner ear or more centrally Flottorp, Morley and Skatvedt concluded from their studies on athetotic children (1957) that the sit of injury was the cochlea. N study on the possible damages in the central auditory tract has, however as yet been published After reviewing the more important acoustic centres, Dr Hall described hi material and his methods The material comprised premature infant from the pediatric department in Oslo who had died from neonatal asphyxia.

In these, the brain had been fixed at a very early stage to avoid postmortal changes. Histologic examination had subsequently been performed at the Anatomic Institute. The cochlear nuclei in the medulla oblongata in particular had shown degenerative changes, and this was common to all the asphyxiated infants. A new technique had been developed which made it possible t express numerically the degenerative changes which might be present. This technique consisted of measurements and drawings of the cochlear nuclei, and calculation of their volume and of the number of cells to each nucleus. Up to the present time 43 infants with asphyxia and six patients who had died without asphyxia had been examined. A considerable loss of cells was demonstrated in the asphyxiated infants. On an average, the cochlear nuclei had lost 48.8% of their cells. Separat examination of each nucleus revealed that the ventral cochlear nucleus had lost up to 41.8% of its cells, while the dorsal nucleus (where the higher tones are supposed to be located) had lost up to 65% of its cells as compared with the control patients who had died without symptoms of asphyxia. Work on the cochlea preparations from the same patient was being done, but as it takes 5 months t make a single temporal bone preparation with modern techniques this work had not yet been completed.

DISCUSSION

D Skatvedt congratulated Dr Hall on his work. She went on to ask whether the difference between patients with spasticity and patients with athetosi had been studied, since hearing loss in the latter is more severe than in th former — *Dr Hall* answered that it was not possible to study this problem at the present time, but that it might be in th future

Meeting November 24 1961

Prof J Anderson, University of Minnesota Minneapolis (By invitation) Some Clinical Conditions Associated with Disturbances in Tryptophan Metabolism

O Knutrud Bladder Neck Obstructions in Children

Obstructions of the neck of the bladder seem t fall int three main groups: (1) Idiopathic contracture of the neck of the bladder (2) Secondary obstruction due to edema and fibrosis following protracted cystitis. (3) Relative occlusion of the internal sphincter in neurogenic bladder often combined with spasm in the external sphincter

True contracture of the neck of the bladder which t present is denoted as idiopathic, must be defined as a functional stenosis of the internal urethral orifice without signs of obstruction in the lower parts of the urethra. On biopsies from the internal sphincter we have found fibrosis in the musculature in 20 of 31 patients. The fibrosis has sometimes extended far into the musculature while the inflammatory changes were limited t the mucosa. It seems likely that submucous fibrosis is secondary to protracted inflammation and that such cases may be classified as group 2. On palpation the internal sphincter feels like strong, but inelastic f brotic ring The finger is invariably easily introduced into the posterior urethra contrary to what is the case in infants with a normal bladder neck. The bladder neck contracture has thus produced an inelastic, fibrotic ring which is t the same time stenotic and insufficient Our diagnostic criteria have been based upon micturition cystography and cysto-urethroscopy together with measurement of the residual urine. Most of our patients have had a moderate amount of residual urine. The presence of 10–20 ml thick, purulent urine immediately following excretion of apparently normal, clear urine has, however been a surprisingly frequent finding in our patients. On micturition cystography concentric constriction of the bladder neck is seen with the posterior urethra dilated below this point The bladder shadow is often irregular and uni or bilateral

reflux is common. Signs of obstruction on the cystogram were demonstrable in 28 of 31 cases; in four cases after repeated examinations. Reflux into the ureters was demonstrated in 19 patient in the same material. W believe that the bladder neck i best evaluated by means of a straight cystourethroscope When inspecting the neck of the bladder from the posterior urethra through this, it is possible to observe that the water pressure causes marked dilatation of the urethra lumen, and the stiff contracted, protruding neck of the bladder is easily discernible In some patients we have performed transvesical suprapubic cystoscopy This revealed that on introduction of water the neck of the bladder contracts in such a w y that the anterior and posterior lips overlap and completely shut the opening The treatment of choice in bladder neck contractures has been open resection with anterior Y-V plasty on the internal sphincter This method ha been employed in 31 patients. In secondary occlusion with edema and fibrosis following protracted cystitis, transurethral resection seems good treatment. In these cases there are no definite signs of obstruction and the resection merely interrupts a vicious circle When we consider the Y-V-plasty as a surgical correction that provides anatomical and functional conditions allowing free and complet urination our results have been good. In *0 patients, postoperative cystography has been done four to six months after operation and the ppearance of the neck of the bladder had in all cases changed into a normal funnel shaped cone

S Halvorsen Oslo

BOOK REVIEWS

E. Rossi (ed.) Postgraduate Courses in Pediatrics. Diagnose und Therapie cerebraler Lähmungen im Kindesalter

S Karger Basel/New York, 1962. Teil 1 72 pages, SFr 9.50- T II 2, 82 pages SF 9.50.

These are the first two volumes in a new series, in which lectures held at Swiss postgraduate courses in pediatrics are published. Several contributors elucidat different aspects of the cerebral palsy problem with emphasis on practical diagnostic problems and therapeutic possibilities. Most contributions are well written and bring the reader up to date with present-day knowledge. Some degree of overlapping could perhaps have been avoided, especially concerning etiological considerations. In the section on the prophylaxis of kernicterus interesting data are presented on the content of A and B blood group substances in various sera, vaccines, hormone preparations and organ extracts. Their importance as possible ABO immunizing agents have probably often been overlooked. The importance of *early* diagnosis of cerebral palsy is rightly stressed. There seems, however to be need for a more critical attitude towards the evaluation of different physiotherapy procedures. Neurosurgery has little to offer as yet to palliate the abnormal tone and hyperkinesias of cerebral palsy- this chapter is one of the best with excellent illustrations. Orthopedic corrections are of greater practical importance and are also well reviewed. In spit of all therapeutic efforts, the final goal seems difficult to reach. t create opportunities for the handicapped, even with normal mental capacity to reach a self-supporting position in society This extremely important social problem could have been dealt with in more detail, although it seems to be just as difficult in Switzerland as in other countries. New volumes of this series of short monographs are in preparation Their appearance will be noted with interest by all who teach and practise pediatrics.

Bo Hellström Stockholm

E. L. Potter Pathology of the Fetus and the Infant.

Year Book Publishers, Chicago, 1961. 2nd edition, $ 22.—

The new edition of the well known text book has been increased in content and volume and now includes conditions relating to infants below one year of age not only to newborns as in the first edition. New material has been added also as regards the fetus and newborn infant. The uthor has now a much broader experience. She has had the opportunity to make observations on over 8000 complet autopsies and in addition has received material from other sources. Principally the contents relate to observations made in the Chicago Lying-in Hospital. In looking through the 650 pages of this nicel printed book one is impressed by the magnificent pictures. As a matter of fact the volume represents more an iconography than a true textbook, the text being somewhat elementary in comparison with the illustrations. It seems as if the author has had special interest in gross malformations to judge from the numerous figures of different kinds of such lesions. There are few histopathologic pictures of organic illnesses of other types. The descriptions of various diseases and

groups of diseases are up to date as is to be expected of a pathologist with such a vast experience in the related fields of childhood pathology The reviewer will, however put a few questionmarks. Hand-Schüller-Christian's disease is listed among the diseases due to inborn errors of lipid metabolism and is regarded as not being related to the other reticuloendotheliosess Letterer-Siwe disease and eosinophilic granuloma. The hypertrophy of the muscle in pyloric stenosis is regarded as present already at birth and the delay in the onset of vomiting to the 2nd or 3rd week of life is explained in the following way: "Vomiting appears only when the mucosa becomes edematous and infiltrated by inflammatory cells because of mechanical irritation produced by passage of milk curds through the narrowed sphincter." Is there really an infiltration by inflammatory cells in the mucosa? The histological changes in the ganglion cells of the diseased muscle layer observed by several Scandinavian authors are not mentioned. The reviewer also misses statement about the simultaneous occurrence of agenesis of the spleen and certain typical malformations of the heart forming as it seems, a disease entity as has been stressed by Ivemark.

This book should be available in every medical library and is strongly recommended to all pediatricians and pathologists, especially those who have a special interest in various kinds of malformations.

A Ashley Weech and Collaborators The McIntosh Era at Babies Hospital, 1931–1960.

Babies Hospital, New York, 1960

This is a commemorative volume to honor Rustin McIntosh for his accomplishments as Carpenter Professor of Pediatrics at Columbia University and Head of the Babies Hospital in New York. The book, which is joy to read for everyone who knows Rustin McIntosh, begins with a bibliography of his 38 publications in the field of pediatrics. An editorial committee of six outstanding pediatricians, former associates of Rustin McIntosh, has chosen 79 articles from about 600 published papers from the Babies Hospital and has reprinted them in this volume. As an introduction a few papers are especially written for the jubilee volume. Dr Douglas S. Damrosch has written a short, humorous biography of "Rusty" and closes the paper by quoting a letter by the Grand Old Man of Pediatrics in the States, Dr Edwards A. Park: Rustin was utterly charming, and had good intelligence which he exhibited quite unconsciously The Babies Hospital was moved from its ancient location at Lexington Avenue to Washington Heights in the neighborhood of the Presbyterian Hospital in 1929 while Herbert Wilcox was medical director and Rustin McIntosh his physician-in-chief Dr Riley gives an account of the many economic difficulties during the first four years when the Great Depression set in and how later on, after McIntosh became Director of the Hospital in 1931 it developed with several new departments: a psychiatric clinic, a pediatric urologic service, a premature center and a neuro-surgical ward. At the same time the Babies Hospital gradually was amalgamated into the Presbyterian Hospital as its Pediatric Department, still maintaining its own laboratories for diagnostic and research purposes. In his chapter "Rusty's Day" Dr Weech has given a narrative about McIntosh wise advice given and of his criticism of the papers of his associates. How he tactfully smoothed out grammatical errors and transgressions against euphony The editorial committee has not only selected the reprinted papers in this nice volume, but has also written some notes on the career the interests and activity at the Babies Hospital of each one of the authors. The book closes with list of all scientific publications during the Rustin McIntosh era and a general index covering the names of the authors and the subjects.

A Kukowka (ed.) Poliomyelitisprobleme.

VEB Gustav Fischer Verlag, Jena. DM 40.20

This book, written in German, contains the *transactions of a meeting held in Dresden* in June 1960 with clinicians, virologists and specialists of rehabilitation from East Germany and other eastern European countries. The chapters on vaccination against poliomyelitis are short, incomplete and give no new results. The vaccination program in these regions was at this time obviously very incomplete. This explains why most of the book deals with clinical aspects of poliomyelitis differential diagnosis, treatment of acute cases, problems of organization, etc. Few results or new ideas are presented. Problems of rehabilitation are dealt with in some detail. There seems to be little of international interest in this book.

Rutger Lagercrantz, Stockholm

G. E. W. Wolstenholme and Maeve O'Connor (eds.): A Ciba Foundation Symposium on Somatic Stability in the Newly Born.

Churchill, London, 1961. 50 s. net.

This symposium was held in early 1961 under the chairmanship of R. A. McCance, whose favourite concept of stability appears already in the title. The bulk of papers read and discussed at this meeting was produced by British colleagues, and the informal mixing of paediatricians and veterinarians, physiologists and biochemists best *illustrates the broad background of neonatal research in their country.* Part of the material published in this book is also found in the recent issue of *Brit Med Bull* (17: 2, 1961) on foetal and neonatal physiology. Nevertheless, both publications should be read by anyone with a serious interest in neonatal research or the clinical care of newborn babies. Apart from British authorities a great number of experts both from Europe and the United States made their contributions to this symposium, not only in presenting data and critical reviews, but also in the most stimulating discussions which follow each paper. Much fruitful speculation and philosophy is to be found in these important parts of the book. Energy metabolism in it broadest sense was the basic subject at this symposium. The effect of starvation of the pregnant ewe on her foetus, the metabolic effects of fasting and food, the development of homeothermy in terms of physics, physiology, biochemistry, endocrinology and enzymology are all different aspects of one and the same basic problem. In this respect this volume alone warrants the old saying that "Man is a unit—not a collection of systems". The volume also contains some long wanted information on the relation between oxygen consumption, on the one hand, and body temperature and ambient oxygen concentration on the other. The clinical implications of these findings is that paediatricians probably will do best by keeping newborn babies in a temperature which is near to the "neutral zone" and at an oxygen concentration which the newborns have to face sooner or later anyway. A few papers have a more direct clinical approach, such as the new regime in dealing with the metabolic changes in the respiratory distress syndrome of prematures (enthusiastically but maybe somewhat uncritically) proposed by Usher. Practically every paper in this book is of a very high standard, either by presenting new data and outlooks, or by giving authoritative summing ups in fields in which the non-expert reader may easily get lost. *This is not a difficult book* and it will help to form, maybe not a platform, but perhaps some fragmentary foundation for a better understanding and thereby better clinical care of the newborn.

Olof Celander, Göteborg

R. MacKeith and J. Sandler (eds.) Psychosomatic Aspects of Paediatrics.

Pergamon Press, Oxford, 1961. 50 s. net

The Society for Psychosomatic Research in London has published these proceedings from a meeting of a study group. Methods of

examination and research in several of the more common psychosomatic disorders of children are dealt with by paediatricians and psychologist and psychiatrists chiefly of the analytic school. Each chapte ends with discussion. In one chapter Anna Freud answers questions from paediatricians. The answers are more interesting than the questions. Miss Freud is less dogmatic and speculative than her interlocutors. She stresses the need of individualization and the importance of illness experiences ("somatopsychic symptoms). The editors and several of the other authors stress that paediatricians dealing with psychosomatic disorders must have good knowledge of child and family psychology "They must become experts in recognizing and relieving tensions as they are in recognizing and treating infections. J Apley writing about recurrent pains (headache, abdominal pain, leg ache etc.) quotes a very low incidence of causal organic disorders. In his series there is commonly a family history of psychosomatic disorders, and contradictory to what has been stated by other writers, the prognosis is often poor many of the children with recurrent pains have adult the same or other psychosomatic symptoms (especially headache)

Even though some of the views of the psychologist and psychiatrists seem to be founded on isolated cases without objective data and highly speculative interpretation, reflecting the problem of ttempting to deal objectively with non-objective material, this is nevertheless useful and thought-provoking book and should be of interest t paediatrician who often encounter these difficult problems.

Rutger Lagercrantz, Stockholm

Hemiplegic Cerebral Palsy in Children and Adults. Little Club Clinics in Development Medicine No. 4.

Published by the Medical Advisory Committee of the N tional Spastic Society London. £1

This volume contains the proceedings of an international study group with participants from most western countries who met in Bristol in lat September In two hundred pages, more than forty papers, including summaries of discussions, have been condensed. This necessarily means that great number of aspects have only been very briefly dealt with and many papers t this meeting were probably just preliminary reports. The reader who has personal experience in the care of children with hemiplegic cerebral palsy will get much out of this book. On the contrary anyone who wants "smooth reading in a field with many controversial opinions will be disappointed.

The few papers dealing with aetiology offer little new material. It is comforting to read the papers by Tizard and Lyon on the early diagnosis of congenital hemiplegia. That a doctor may not be ble to diagnose this major neurological stat until a "free interval of several months ha passed is obviously due to the dormant activities of the cerebral hemispheres t this stage of development. "The dog is not able t speak, because the dog has nothing t say The great clinical value of the one-sided tonic neck reflex as early evidence of hemiplegia is stressed.

Growth disturbances of the affected limbs, and intellectual, visual and perceptual disabilities have been penetrated. One of the more extensive reports is that by Ounsted on the EEG-findings in relation to subnormality

The urgent need of assessing treatment was stressed by several uthors, both as regards physiotherapy orthopaedic surgery and neurosurgery Kendall' st tement that Many children in this country are receiving treatment not because of its value or even becs se t is pleasant for the child, but simply because t is felt that something must be done is probably alid in most countries. However few uthorities oppose training and physiotherapy early in the course of hemiplegia. Pollock specifies criteria for successful orthopaedic surgery and stresses the necessit of an accurat diagnosis and assessment of the hild handicap both prior t and after surgery The poor long term

results of intra-abdominal obturator neurectomies are surprising. Carmichael reports 44 cases in which hemispherectomy had been carried out About half this group showed to have a large cyst in the distribution of the middle cerebral artery Why? Intelligence and behaviour were little affected, whereas convulsions were radically reduced

In spite of the obvious shortcomings in presenting *experiences and views on a subject* as highly controversial and with so many aspects as cerebral palsy just as a report of a symposium, the present volume should be consulted by every doctor responsible for the care of these children. The uncritical reader may find support of some kind for practically every personal belief The more critical reader will probably agree with those authors who claim that the final word on aetiology diagnosis and treatment of congenital hemiplegia has by no means been spoken, and that critical assessment of findings and results as well as controlled studies are urgent needs.

Olov Celander Göteborg

The Development of Homeostasis. Symposia CSAV Editor P Hahn. Publishing House of the Czechoslovak Academy of Sciences. Prague 1961

In order to bridge the gap between the natural sciences in East and West several symposia have been held in Czechoslovakia during recent years with participants from both hemispheres and in this respect Czechoslovakia has not only the advantage of a strategic position from the geographical point of view but it is particularly well suited for this important task, owing to its high scientific standard.

For three days in September 1961 a symposium was held in Czechoslavakia on the subject "The Development of Homeostasis, with special reference to factors of the environment" Participants were investigators from Canada, Czechoslovakia, England, Hungary U.S.A and U.S.S.R. Several of the papers were given by members of the big Institut of Physiology in Prague. The chairman was Prof E. F *Adolf from* Rochester U.S.A., and both the papers read at the symposium and *the discussions are* included in this book. The present symposium was somewhat similar to the Ciba Symposium on "The somatic stability of the newly born" held in London in 1960, but in the present book more emphasis has been placed on experimental studies in animals *and on problems related to comparative* physiology The main subjects of the book fall into the following categories homeostasis, its development and evolution; water and electrolyte metabolism, phylogenetic and ontogenetic aspects; the development of acid-base control; nutrition and homeostasis; nutrition and longevity; and the effect of undernutrition at the cellular level. All in all a fine book of particular interest because several of the papers and the underlying philosophy show a somewhat different approach to the problems than is usually found in the West.

Bent Friis Hansen, Copenhagen

Walter Siegenthaler: Klinisch Physiologie und Pathologie des Wasser und Salzhaushaltes

Vol. 9 of *Patholog und Klinik in Einzeldarstellungen.* Springer-Verlag, Berlin, Göttingen, Heidelberg, 1961 175 p. Price 49.4. DM.

A number of books have been published in the last few years about water and lectrolyte metabolism in general. The present book, however deals chiefly with problems related to aldosterone, oedema and diuretic drugs. The author is "Privatdozent" at the medical out patient clinic at the university in Zürich. At first he gives a short up-to-date discussion of the physiological aspect of the metabolism of water and electrolytes. Although it is rather short, this chapter contains the most pertinent data from the clinical point of view It is followed by a brief account of kidney function and the regulation of homeostasis, including the action of the antidiuretic hormone which mainly governs the osmolarity

of extracellular fluid via the osmoregulatory centers in hypothalamus. This regulation is summarized in a few very clear diagrams.

After this introduction the author turns to the main object of his book and he has succeeded in giving a lucid picture of the physiology of aldosterone and the role played by this substance in oedema of different aetiology. The author himself has made fine contributions towards a better understanding of the regulation of aldosterone production and based on these observations he discusses how a combination of modern diuretic drugs and aldosterone—antagonists can be used with advantage in the treatment of certain categories of patients with oedema. The excretion of aldosterone in the urine seems to vary proportionally to changes in the oedema rather than to the absolute size of these, that is, a large increase of urinary aldosterone is found during the process of fluid retention. Once a steady state has been reached the excretion of aldosterone may decrease again to normal values, and even lower values are found when diuresis sets in and the oedema fluid is being mobilized. This observation is explained by the theory that aldosterone is not the primary factor in the formation of oedema, but the first step in this is a loss of fluid from the "vascular bed" into the "interstitial space". This leads to a reduction of the blood volume whereby centers in diencephalon are being stimulated via receptors in the right atrium and the arteria carotis communis and compensatory hyperaldosteronism sets in in order to re-establish a normal blood volumen. The result is sodium retention and further fluid retention is made possible by compensatory antidiuresis due to a secondary release of antidiuretic hormone. Only in patients with cardiac decompensation, this theory does not seem valid since these patients from the beginning have an increased blood volumen. This difficulty can be overcome however by assuming that a primary hypovolaemia is found in the arteria carotis communis section of the "vascular bed". This may well be true but as long as we do not know the true nature of volume regulation of the body fluids, it is not possible to give any definite answers to these important problems.

The final section of the book is a brief but clear description of the mode of action of different kinds of diuretics and how their effect in certain cases can be enhanced by the use of the aldosterone antagonists. The clinical application of this interaction is discussed. Since disturbancies of water and electrolyte metabolism enter into most branches of paediatrics, this book can be highly recommended to all clinicians as a short and very easily read presentation of complex problems which relate to every-day's medical problems.

Bent Friis-Hansen, Copenhagen

M. Timmer: Child Mortality and Population Pressure in the D. I. Jogjakarta, Java, Indonesia.

A social medical study. Diss. Amsterdam.

Jogjakarta lies in the middle of the south Java coast. The population in 1930 was 1.56 million, i.e. about 4% of the total population of the island. The author during a 6-year period as a doctor in a pediatric department in the region, collected a large mass of data which are now presented as a thesis.

Part I, containing 6 chapters and 145 pages, deals with demographic aspects. Part II, consisting of 10 chapters and the remainder of the 300 page volume concerns medical aspects.

The infant mortality is difficult to assess, but is estimated as 15%. The corresponding figures for children of pre-school and school ages are estimated as 4.3% and 0.7% respectively. From a material of 1200 deaths in two pediatric clinics in Jogjakarta during the years 1954–58, the author draws the conclusion that the leading cause of death is malnutrition followed most closely by diseases associated with diarrhoea. In the first month of life a low birth weight and tetanus appeared to be the most prominent causes of death.

The last chapter in the book deals with "Responsible parenthood and birthrate" There is much to be done in this part, as in many other regions of the world. The quotation (J H. Bavinck) with which the chapter opens is of interest.

"The J vanese lacks the strong adaptation to Western life, one finds in the Japanese H also lacks the economical instinct f the Chinese The great transition with him goes with more stiffness and greater difficulty and the old life keeps functioning longer and with greater intensity

Even so many movements may pass along sid and over him, inwardly he remains the same H is inclinded to keep somewhat aloof and notwithstanding all adaptation on the outside, in the depths of his soul he remains his old self.

Bo Vahlquist, Uppsala

J Ströder (ed) Pädiatrische Fortbildung

J F Lehmann, Munich, 1962. Price DM. 4.–

The rapid progress of todays medicine and the difficulties of following the new advances as they are presented in the current literature have made the publication of surveys of different types more and more necessary A recent contribution to this ever increasing family of review volumes is the *Pädiatrische Fortbildung* by J Ströder with collaboration of several well known German paediatricians. This book is written not only for the paediatric specialist but also for the general practitioner interested in children and intended as a postgraduate course in important paediatric topics. Some of the chapters deal with a major symptom as "the yellow child "the nervous child "the thin child" etc. In other chapters clinical entities are treated in the usual way and more important recent advances are stressed. Several authors have made historical notes and illustrated the chapters with instructive case reports from their own experience. A large part of the volume deals with endocrine diseases in childhood and related disorders. The last chapter is dedicated t surgical problems of the newborn.

The references following each chapter are mostly up to date even if in some cases one could have wished more of original articles and less of older monographs and surveys.

This volume is the first of a series to be published.

C G Bergstrand Stockholm

Lee E. Farr H W Knipping and William H. Lewis Clinical Aspects of Nuclear Medicine.

Westdeutscher Verlag, Cologne and Opladen, 1961 486 pages. Price DM. 49

This volume contains thirty three papers given at the Symposium on Clinical Aspects of Nuclear Medicine held in Cologne and Julich in 1961 The contributors represent most Western countries. The papers are mostly short reviews or accounts of recent developments in a large number of various fields in nuclear medicine, of which the following may be mentioned. radiation therapy with kilo-Curie sources and thermal neutrons, production of radioisotopes for medical use radiation damage and control in the clinic, the use of analogue computors in evaluation of radiotracer data and the use of radioisotopes in clinical diagnosis. Of specific interest are the discussions on the development of nuclear reactors more or less specifically intended to serve medical research, i.e. the production of suitable isotopes and new sources of irradiation. The book offers a fairly good review of the present situation of nuclear medicine to readers with some knowledge in this rapidly growing field.

L. Garby Uppsala

Acta Paediatrica 51, 481—489 Sept. 1962

Institut for Mother and Child Care Institute of Physiology of the Czechoslovak Academy of Sciences and Infant Home Prague Czechoslovakia.

Changes in the Blood Levels of Lipid Metabolites and Glucose Following a Fatty Meal in Infants[1]

by V MELICHAR, M. NOVÁK, P HAHN O KOLDOVSKY and L. ZEMAN

Fat appears to be of particular importance for infant mammals as is indicated by the fact that milk contains usually more fat than the solid food consumed by adults (Table 1) In agreement with this, the RQ of newborn infants during the third to fifth postnatal days indicates a preponderant utilization of fat for energy purposes [33] (80-90% of the nutrients utilized) This was demonstrated for infant rats [9 10 11], in which fat utilization during starvation is much higher than in adults of the same species.

It seems, however that fat is also metabolized in a qualitatively different way by infant mammals than by adults. This was the conclusion from previous experiments [1 10 11 17 18 36 37], in which fat absorption from the intestine nd fat utilization were studied in infant rats

In the work presented here similar differences were looked for in human infants. Blood levels of lipids and glucose were studied during f t absorption. These are a fairly good indicator of processes occurring during absorption [8]. Although changes in blood lipid levels have been studied repeatedly in infants [3, 4 14 20 31 32 33] usually only one stage of development was included and the newborn period as such was not often studied.

Methods

Table 2 summarizes the groups of infants studied. All infants were healthy and were in hospital or in an infant home during the time f the experiment Newborn infants received the fatty meal by stomach t be, the others from a bottle or by spoon. All infants that vomited part f the administered dose were excluded from the evaluation. Tolerance f the fatty meal was good. Only some infants aged –3 months receiving free fatty acids from cream showed change in the quality of the stools without any other signs.

The newborn infants (1 day old) received the test dose as the first food in their lif on the average 15 hours fter birth. Older infant were always fed in the morning after having had their last meal 8–10 hours previously

Standard errors were calculated in the usual way

$$sx = \sqrt{\frac{\Sigma(\bar{x} - x_1)^2}{n(n-1)}}$$

The difference in the course of the curves wa evaluated using the so-called "pair test

$$t = \sqrt{\frac{M_1 - M_2}{C}}$$

[1] Preliminary report: Melichar *et al.* [23].

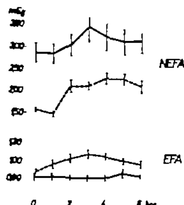


Fig 2. Changes in NEFA and EFA after administration of free fatty acids cream. Twelve newborn infants, 14 infants. Upper half of figure: ordinate NEFA mEq/100 ml, lower half of figure: ordinate EFA mEq/ml. Abscissa: time in hours. Full line: 1-day-old newborn infants (A), dashed line: infants aged 2–3 months (B). Vertical lines denote SE.

NEFA: $p < 0.002$ for maximum in any hour in group A, $p < 0.05$ for hour 4 in group B. EFA, $p < 0.01$ for hour 2 only in group B

groups while EFA levels only rise in 2–3-month-old infants.

After both EFA and NEFA administration a rise in blood glucose was found in the youngest age group while in older children the usual fall was found (Fig. 3).

(3) *These experiments were repeated with olive oil* since the rise in blood glucose might have been due in some way to the rather large percentage of carbohydrate present in cream. It is apparent from Fig 3 that olive oil administration is again followed by a rise in blood glucose level in newborn infants, while later in life the level falls. Hence the rise in blood glucose level in the youngest age group is not due to the carbohydrate contained in cream.

Changes in EFA blood levels after olive oil differed somewhat from those observed after cream administration. The EFA level rose even in the youngest age group, but only after 6 hours (Fig 4)

(4) *Chylomicrons* On visual inspection the serum from newborn infants never appeared opalescent and the EFA level in those children did not increase after

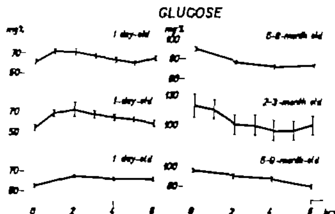


Fig 3. Changes in blood glucose levels after cream, free fatty acids cream and olive oil. Left half of figure from top to bottom: 6 newborn infants after cream (A), 12 newborn infants after free fatty acids cream (B), 11 newborn infants after olive oil (C). Right half from top to bottom: 8 infants 6–8 months after cream (D) 6 infants 2 months after free fatty acids cream (E), 7 infants 6–10 months after olive oil (F) Ordinate: mg % of glucose abscissa: time in hours. Standard error indicated by vertical lines. Significance of individual curves was calculated by the pair test (see Methods).

Glucose: for group A $p = 0.002$ for the rise in the 1st h for group B, $p < 0.05$ in the 2nd hr for group C, $p < 0.01$ in the 2nd hr For group D $p < 0.001$ for the decrease in the 4th hr; for group E, p at the border of significance in the 4th hr; for group F $p < 0.01$ in the 6th hr

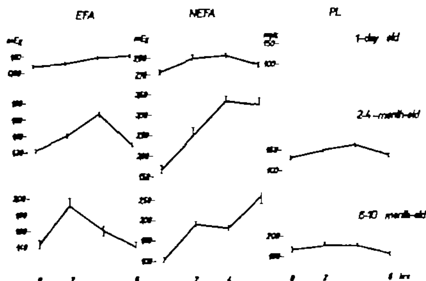


Fig. 4. Changes in the levels of lipid metabolites in blood serum during absorption of olive oil. From top to bottom: 11 newborn infants aged 1 day (A), 9 infants aged 2–4 months (B), 7 infants aged 6–10 months (C). EFA, NEFA, PL marking as in Fig. 1

EFA: for group A, $p < 0.05$ in the 6th hr; for group B, $p < 0.01$ in the 4th hr; for group C, $p < 0.05$ in the 2nd hr. NEFA: for group A, $p = 0.02$ in the 4th hr; for group B, $p < 0.001$ in the 4th hr; for group C, $p < 0.02$ in the 6th hr. PL: for group B, $p = 0.05$ in the 4th hr

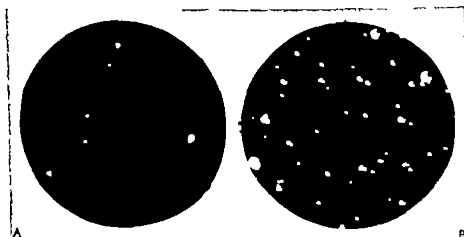


Fig. 5. Chylomicrons in the blood after human milk. Method of Orklits [22]. Microscope Lumipan-Zeiss, dark field, double immersion. 1350. (A) Chylomicrons in blood of 4-day-old infant. (B) chylomicrons in blood of 6-day-old infant

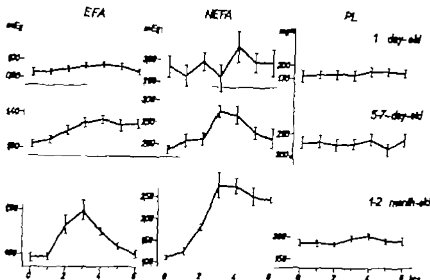


Fig. 6 Changes in the levels of lipid metabolites in blood serum during absorption of breast milk cream in premature infants. EFA, NEFA, PL marking as in Fig 1 *Six infants in each group.* From top to bottom, infants aged 1 day (A), 5–7 days (B), 1 2 months (C).

EFA: for group B, $p < 0.05$ in the 4th hr; for group C, $p < 0.02$. NEFA: for group B, p 0.01 in the 3rd hr; for group C, $p < 0.01$ in 3rd hr.

cream chylomicrons were looked for in the blood of some infants 2–3 hours after the last normal meal. They were never found in infants younger than 4 days and after that day they gradually increased both in size and number (Fig 5)

(5) *A group of premature infants was also tested* They received cream in the same way as is described above. The same sequence of changes was observed so that 5–7 days after birth *EFA levels* rose and *chylomicrons* appeared (*Fig 6*)

Discussion

The above experiments confirm and extend previous observations in rats [10 11] They show that there is a particular interrelationship between fat and carbohydrate metabolism in the newborn period. At that time administration of fat results in a rise in the blood glucose level a phenomenon which does not occur in adults In rats this period is followed by a stage when liver glycogen levels rise in response to olive oil administration [10]. Obviously this is difficult to verify in human infants Since in other respects, however reactions appear similar in the two species it is quite possible that this later response also exists in human infants.

The experiments with olive oil *show that the rise in blood glucose is not due* to the carbohydrate present in cream. Hence a special mechanism must be at work during the first week of postnatal life. This is probably not related to nor adrenaline secretion, since that would lead to a rise in *NEFA* and glucose In addition administration of glucose decreases the level of NEFA in the blood [?7]

The administration of a fatty meal does not result in a rise in the level of EFA in

the blood although that of NEFA increases in one-day-old infants. This might indicate an inability of the intestinal wall of newborn infants to esterify or re esterify free fatty acids absorbed from the lumen to the same extent as later in life where this ability has been demonstrated [2, 15]. Experiments in rats seem to con firm this view since histologically the wall of the intestine in this shows only slight esterase activity in very young animals [1]. In addition chylomicrons, the typical form in which triglycerides are transported, could not be demonstrated in newborn infants, rats or puppies (unpublished observation) It must be born in mind, however that the level of EFA does increase even in newborn infants 6 hours after olive oil administration. This may be explained in two ways. Less probably olive oil in contrast to cream, is broken down in the lumen and resynthesized in the intestinal wall, or more probably some of the triglyceride is transported across the intestinal wall as such, without being broken down first in the lumen. This latter view is supported by the fact that proteins pass through the in testinal wall intact in newborn mammal [1].

Two distinct periods can be observed in the development of the reaction to a fatty meal. The first has been discussed. The second is found to occur after bout the 3rd month of postnatal life. At that time administration of cream leads to a rise in the level of phospholipids in the blood and in addition the level of NEFA rises only slightly This is the usual d lt response and seems to indicate that these children are perhaps at the end of the natural weaning period. Further work is required to elucidate this point which seems very important in view of the fact that in rats changes in the diet occurring during weaning period are reflected throughout life [19 *0 1].

It may be pointed out that premature infants show the same kind of development so that the moment of birth and the subsequent supply of a special kind of food seem to be more important than the chronological age From that aspect the time of weaning may be very important since at that time the composition of the food is changed permanently

Summary

Changes in the blood levels of EFA, NEFA, PL and glucose 1 –, 3 4 5 and 6 hours following the administration of either cream from human breast milk or free fatty acids prepared from breast milk or olive oil (1.5 g/kg) have been stud ied in infants at ages one day 5–7 days 1–4 months and 6–10 months. NEFA levels rise in all age groups, particularly in younger infants, with maximum levels at 3–4 hours, while EFA levels follow the same time course of rise in all age groups with the exception of one-day-old infants, where no rise occurs with cream or free fatty acids, after olive oil a small rise was observed only after 6 hours. Chylomicrons were not observed in infants younger than 4 days of ge Rises in PL following cream were seen only in infants. Following hu man milk cream human milk fatty cids and olive oil, blood glucose rose in new born infant but fell in older infants. Th find ings are discussed from th viewpoint of the development of fat metabol sm in infant (esterification and transport mech anism)

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Institute for Mother and Child Care
Karla Marxe 157
Praha 4-Podolí
Czechoslovakia

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From the Central Hospital for Infectious Diseases (Director Dr J Román) Budapest, Hungary

Ventilation Studies in Pneumonia of Infants and Children

by D BODA and L. MURÁNYI

In the literature on respiratory function, which is growing at an enormous rate relatively and surprisingly scarce evidence is found concerning the disturbance of respiration in pneumonia especially in that of infants and children. Direct measurements have been published only by Salkov [13] and Maslov [9] This is the more surprising if we realise that the problem is gaining significance because of the increase in the incidence of antibiotic-resistant, severe, life-endangering forms The picture of the pneumonic respiratory function is obscure even if we count to it the reports dealing in general with restrictive pulmonary processes physiologically similar to pneumonia [15 16] and the literature on the respiratory distress syndrome of the newborn studied in more detail in paediatrics [5 7 8 10] and on the pulmonary changes associated with cystic fibrosis of the pancreas [16]

Apart from the scarcity of pertaining evidence the present studies of ours have been justified by the circumstance that ventilation was examined by a method not requiring the patient s collaboration [1]. The significance of this is obvious, especially in the restless, apnoeic infant and child

Methods and Case Material

The CO_2 output per minute ($\dot V_{CO_2}$), the CO_2 *content of expired air* ($C_{E CO_2}$), *the arterial* CO_2 tension (P_{CO_2}) were directly measured, the latter by the gastric balloon (*gastrotonometric*) *method. From these data we obtained* by calculation the values f minute ventilation ($\dot V_E$) alveolar ventilation ($\dot V_A$), the tidal volume (V) the physiological dead space (V_D) the ventilation equivalent (E) and the percentage dead space (V_D/V). The procedure the critique of the method and the results obtained in normal children of comparable age have already been described [1].

A total of 70 examinations have been made in different stages of the pneumonia of a total of 21 infant and small children Five of the patients was less than 1 year old, *11* were 1 to 3 years old and the remaining six were older than that. To facilitate evaluation the f llowing grades of severity of pneumonia have been set up. In the severest *group (designated* ●) the patient's condition was characterised by a maximum respiratory ffort and by a gradual decline In the next grade (designated ◐) the clinical symptoms were marked, but the *patient* condition was no longer critical. In the group milder than this (designated ○) the pneumonia could be *diagnosed only* by physical or radiological examination at the time of testing and was not accompanied by systemic *symptoms*. In the latter stage (designated) the patient was convalescing, and was clinically cured.

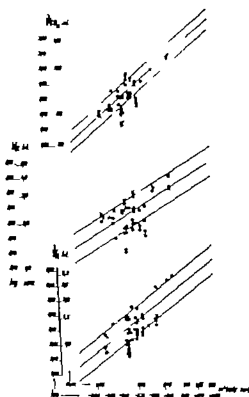


Fig. 1 Correlation of CO output per minut ($\dot{V}_{CO_2}$), minute ventilation ($\dot{V}_E$), and alveolar ventilation ($\dot{V}$) with the body surface in pneumonia of the child. The solid lines show the regression equation and scattering of the normal correlation of these values with the body surface. Signs: Severest stage ● Moderately severe forms ◐ Mild forms ○ Convalescence

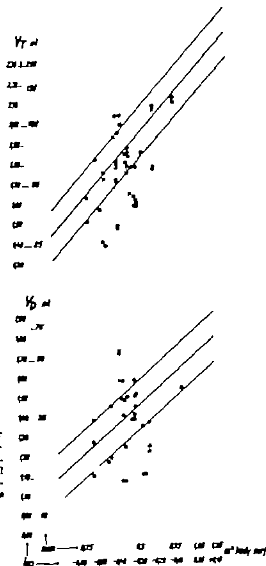


Fig. 2. Correlation of tidal volume (V_T) and dead space (V_D) with body surface in pneumonia. Signs as in Fig. 1

The basic illness was bronchopneumonia, so common in paediatric practice and due usually to influenza or other respiratory infection

While in the severe condition, the patients were treated with selected broad-spectrum antibiotics, combined with penicillin and streptomycin, parenterally Those in the critical stage were subjected t pharmacological hibernation without external cooling, and were given in several portions 2 to 3 mg/kg of a cocktail of Largactil Dolantin Phenergan The same patient were treated also with cortisone, in the usual 5 mg/kg dose daily

Results

The results are presented in Fig. 1 to 4 and in Table 1 and 2. The data are compared with the ones obtained in normal subjects. In previous studies [2] we found namely in 83 normal children of different ages that the data examined could be expressed in relation to the body surface area and age, respectively in the form of regression equations and that the correlation was linear in the double logarithmic system. In the figures here presented we give the straight line expressing normal correlations and the scattering around the regression curves (± 1 s) and in this background are drawn up the data for the pathological cases, with the corresponding designations. Thus, the figures indicate the numerical data of the pathological cases, as related to the normal values, and according to the grades of severity. Just as with the studies on normal subjects, we present here also the values for $\dot{V}_{CO_2}$, $\dot{V}_E$, $\dot{V}_A$, V_T and V_D in relation to the body surface area and those for P_{CO_2}, $C_{E_{CO_2}}$, f, R, V_D/V_T in relation to age. The table serves to facilitate comparison of these same data. In Table 1 we show in how many cases we measured values within the range of normal regression, or ones larger or smaller than that.

TABLE 1. *Pneumonia of the child. Divergence from the physiological mean of the principal data of ventilation*

Explanation: / *signs* $\dot{V}_{CO_2}$ CO production per minute. $\dot{V}_E$: minute ventilation. $\dot{V}_A$: alveolar ventilation. V_T: tidal volume. V_D: dead space. P_{CO_2}: intragastric CO tension. $C_{E_{CO_2}}$: CO_2 content of expired air. f: respiratory rate. R: respiratory equivalent. V_D/V_T: percentage dead space. ● severest stage, critical condition. ◐ manifest clinical symptoms. ○ physical and radiological signs and symptoms only. symptom-free convalescence. ++ deviation from the physiological mean exceeding 2 s. + exceeding 1. ± exceeding physiological mean within 1 s. ∓ smaller than physiological mean within 1. − smaller than physiological mean over 1 s. **−** smaller over 2 s.

	Stage	++	+	±	∓	−	**−**	Total
$\dot{V}_{CO_2}$	●	—	1		3	2	2	10
	◐	—	3		8	5	3	20
	○	—	8	5	6	8	3	23
		—	2	4	5	1	1	13
$\dot{V}_E$	●	3	—	2	3	—	2	10
	◐	3	3	6	2	5	1	21
	○	1	4	7	6	5	3	28
		—	3	4	3	2	1	13
$\dot{V}_A$	●	—	1		2	3	1	9
	◐	—	3	5	7	8	—	20
	○	—	6	3	8	7	2	26
		—	2	3	4	3	—	12
V_T	●	—	1	—	2	1	6	10
	◐	—	2	—	6	3	8	21
	○	—	1	6	7	8	3	[illegible]
		—	1	4	3	3	1	12
V_D	●	1	1	2	1	2	3	10
	◐	3	1	4	3	3	6	20
	○	1	5	3	6	4	7	29
		1	2	1		4	3	11

Evaluation and Discussion

The CO production per minute sheds light essentially on the condition of energy metabolism. As can be seen, values outside the physiological range were measured in just a few cases. Most of the data were within that range but in a considerable percentage of the cases energy metabolism was low as it was indicated by the CO_2 production values. In this, treatment with the cocktail lytique may have played a role. However according to the investigations of Varga & Mestyan [14] it is more likely that the low metabolic rate is a result of a direct regulatory activity of hypothalamic centres.

According to our data minute ventilation did not decrease: a failure of ventila-

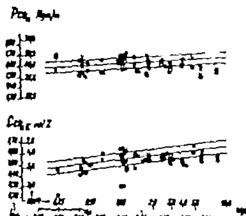


Fig. 3. Gastrotonometric CO_2 tension (P_{CO_2}) and CO_2 content of expired air ($C_{E_{CO_2}}$), plotted against age in pneumonia. Signs as before

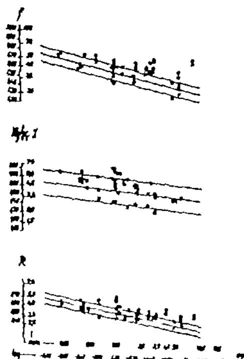


Fig. 4 Correlation of respiratory rate (f), percentage dead space (V_D/V_T) and ventilation equivalent (R) with age in pneumonia. Signs as before.

Table _. Pneumonia of the child. Divergences from the physiological norm of the principal data of ventilation (Explanation of signs see Table I)

	Stage	+ +	+	±	∓	–	=	Total
P_{CO_2}	●	2	1	3	1		—	9
	◐	—	4	7	1	2	3	18
	○	—	1	8	5	7	4	25
		—	2	3	6	3	1	15
CO_{2E}	●	—	1	1	3	1	3	9
	◐	—	1	2	6	7	4	19
	○	—	1		10	5	4	22
		—	1	3	4	1	1	[illegible]
f	●	5	1	2	1	—	—	[illegible]
	◐	7	6	3	1	1	—	[illegible]
	○	4	9	4		3	—	22
		—	2	5	4	2	—	13
R	●	3	—	3	2	1	—	[illegible]
	◐	6	5	5	3	1	—	[illegible]
	○	4	4	8	5	—	2	23
		—	4	5	8	1	—	13
V_D/V_T	●	2	4	2	1	—	—	[illegible]
	◐	—	5	11	1	—	1	18
	○	—	2	10	6	3	—	21
		—	—	8	3	2		13

tion cannot be spoken of in pneumonia, on the contrary in the more severe phase higher V_E values were characteristic which was made even more marked by the comparison with th V_{CO_2} values which were usually lower

Alveolar ventilation, which indicates the true effect f ventilation, was less increased, in most cases it was within normal limits t the peak of the severe condition, signifying thereby that in pneumonia there is no failure of ventilation in this sense in the most critical phase of the disease either

According to our data the most characteristic change in the disturbance of ventilation in pneumonia is a marked decrease of the tidal volume In the two severest

groups values higher than the normal mean were measured in three cases only but, as shown in Fig. 2 in the same cases the dead space was also considerably increased. All the rest of the V_T values in those groups were lower than the physiological mean, in several cases the values were very low. This means that on one inspiration very little air can enter (in spite of the deep jugular intractions) the lung of the patient with pneumonia, fighting to survive.

This evidence is even more relevant if we analyse it against the simultaneously determined physiologic dead space values. In pneumonia the physiologic dead space varied over an even wider range than normally: in the two groups containing the most seriously ill patients values much higher and much lower than the physiologic mean occurred equally. The higher dead space values are understandable; the ones substantially lower are surprising. This must be so, however, for in certain cases the tidal volume was so reduced that it was smaller than the dead space volume characteristic of the patient's age. Theoretically, this would mean that no gas exchange could take place any longer. That there still is gas exchange is explained by the fact that intrapulmonary pressure varies greatly during the fast breathing. As a result air is flowing in the respiratory pathways with an explosion like rapidity and thus the gas exchange takes place chiefly in the centre of the respiratory pathways, and this causes the apparent decrease of dead space. But even this smaller dead space represents a higher percentage of the tidal volume which is diminished anyway: the V_D/V_T ratio being unfavourably high in such cases too (Fig. 4).

The value for P_{CO_2}, approaching the conditions prevailing in the arteries, merits particular attention by its significance in respiration studies. As is clear from Fig. 3 even a minor CO_2 retention is uncommon in pneumonia, there is rather a tendency to hyperventilation. These cases of ours, in which there is an excitation of the respiratory centre, seem to bear a resemblance to the overventilation syndrome of Rapoport [11].

The changes in ventilation just outlined make it understandable that the CO_2 content of expired air is usually lower; the ventilation equivalent is often unfavourably high and the respiratory rate is significantly increased during the severe phase in harmony with the well-known symptom of pneumonia.

The changes we have found in the V_E and V_T values agree with the values obtained by the mask method in pneumonia by Salkov [13]. Essentially similar results have been obtained in the cases of infantile respiratory distress syndrome [7, 10] and in those of chronic respiratory failure associated with cystic fibrosis of the pancreas [6]. The characteristic nature of the reduced V_T is indicated by the interesting lung model experiment of Zellhofer [15], in which the characteristics of the restrictive disturbance of ventilation, essentially identical with the respiratory disturbance in pneumonia, could be induced specifically simply by narrowing the capacity of the lung model, i.e. by narrowing the V_T and leaving other factors unaltered.

In our investigations we ascribe the greatest significance to the changes that concern the poor ventilation in the patient with severe pneumonia. All of them indicate that in the organism affected by

pneumonia the gas exchange essential for life goes on under most unfavourable circumstances, which ultimately results in an extreme increase of respiratory effort. There seems to be no doubt therefore that the statement according to which dyspnoea is a symptom of the increased effort to continue breathing [1] applies also to pneumonia and that the observations made by Cook *et al.* concerning the respiratory distress of the newborn are valid in general in the case of the respiratory disturbance of pneumonia, according to which death is ultimately caused by total exhaustion.

In conclusion we should like to deal with the practical aspects of our results. When recognizing the significance of the increased respiratory effort Cook *et al.* [5] made it clear that therapy should aim at replacing or supporting the forces involved in that effort. Among the modern therapeutic methods the one involving curarization combined with intermittent positive pressure respirator treatment seems to be the most effective. As we have already reported [3] the experience obtained in the treatment of the severest forms of pneumonia seems to confirm this view in practice too.

Summary

The principal data of ventilation have been determined on a total of 70 occasions in 21 cases of severe pneumonia of the infant and the child. In pneumonia hypercapnia is an exceptional occurrence there being rather a tendency to hyperventilation. The patient has to carry out gas exchange under most unfavourable circumstances. Severe pneumonia is characterized by a considerable diminution of the tidal volume and in addition also the percentage of the dead space within it is greater. The maintenance of ventilation requires a greatly increased effort, which may ultimately lead to a total exhaustion. As a plausible practical conclusion that may be derived from the results obtained it is suggested that in the severest forms the respiratory effort should be aided by lasting respirator treatment.

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Central Hospital for Infectious Disease
Gyáli-út 5–7
Budapest IX
Hungary

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From the Department of Paediatrics, University of Göteborg, Göt borg Sweden, and the Biochemical Research Laboratory Kolonien Filadelfia, Dianalund, Denmark

Familial Neutropenia Possibly Caused by Deficiency of a Plasma Factor

by JAN BJURE, LARS R. NILSSON and CLAUS MUNK PLUM

Familial neutropenia is an uncommon condition, of which the following types are recognized.

1 A familial tendency to moderate tropenia, transmitted as a dominant but usually without marked signs or ms [4 5 9].

2 Infantile genetic agranulocytosis, transmitted by an autosomal recessive gene [1 16]. The neutropenia here is extreme Severe infections appear soon after birth, and usually lead to very early death.

3 Severe familial neutropenia with recurrent infections of varying severity but with rather good lif expectancy [13 17]. The mode of inheritance seems to be dominant.

4 Chediak Higashi–Steinbrinck s disease—neutropenia in individual with atypical albinism, bnormal gran la in the leucocytes and giant incl sions in a number of monocytic cells [2 11] It course is characterized by greatly reduced resist ance to infections which lead to f tal outcome

5 Neutropenia without other blo l changes has been described in a number of relatives to at least ? patients with Fanconi's anaemia [8] Neutropenia has also been noted in relatives of patients with idiopathic aplastic anaemia, in numbers which can hardly be co-incidental [14].

6 Cyclical agranulocytosis has appeared familially in a few cases [10 33]

Other reported cases of familial neutropenia [28] cannot be fitted exactly into any of the above categories. Further classification may be possible in the future

This article is a study of two brothers with chronic neutropenia possibly caused by deficiency in th plasma of a factor necessary for myelopoiesis.

Case Reports

Both parents were healthy and unrelated They had four children, two healthy girls born in 19.0 and 1933 and tw boys born in 1948 and 1951 the patients described here

A brother f the paternal grandmother had died f malignant lymphogran lomatosis. A paternal second usin was weak in health and physically resembled the lder b y The mother had a half brother in wh mo derat pancytopenia was not l the aetic logy was uncerta but was p ss bly the result f myelofibrosis.

TABLE 1 *The leucocyte levels and differential counts in the elder boy L. O*

	White blood cells, per mm³	Immature cells, %	Stab cells, %	Segmented neutrophils, %	Eosino-phils, %	Baso-phils, %	Lympho-cytes, %	Mono-cytes, %
May 1950	8700	—	0	13	0		84	1
Sept. 1950	8800	—	1	15	3		74	7
July 1952	4000	5	3	6	9	2	54	18
Feb 1953	*700	5	.5	10			58	
	3200	2	4	3	14		57	10
March 1953	6400	8	22	6	0		30	28
	3500	3	1	9	9	1	63	12
	2800	4	2	7	15		7*	8
Sept. 1953	6800	7	*6	11	1		44	11
Nov 1956	5400	—	4	7	8		62	.1
March 1958	3000	—	1	7	3		74	15
July 1958	3800	5	1	10	8	2	40	8
Dec. 1958	4200	—		–	18	1	47	32
Jan. 1959	6900	—	3	9.5	18	1.5	45	23
March 1960	8300	—	7	14	15		45	19
Oct. 1960	5800	—	2	16	1	1	44	13

Case I

L. O., born 28/*/1948, aged 13 years. Pregnancy and delivery normal, birth weight 2750 g. Motor development was delayed: he could sit unsupported at 9 months, and began walking at 2 years. His performance at school was poor.

The boy had always appeared delicate. H was constantly tired and had recurrent bout of fever with or without other symptoms. There were frequent throat infections and attacks of diarrhoea. Small injuries had shown poor healing tendency, becoming indurated, and sometimes persisting for a month or more. From the age of 2 years, the gums had shown inflammatory swelling and were foul-smelling. He often complained of aching in his arms and legs, worst in the fingers.

Neutropenia was first noted at 2 years of age and had persisted ever since (Table 1). In 1952 he was admitted t hospital under

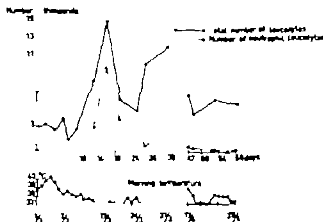


Fig. 1 The clinical course of the measles in patient L. O

TABLE 2. *The leucocyte levels and differential counts during the illness period after morbilli in 1953 in the elder boy L. O*

Date	White blood cells, per mm³	Immature cells, %	Stab cells, %	Segmented neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes, %	Monocytes, %	Plasma cells, %	Sedimentation rate
1/3	3,000		1	7	3		74	15		22
3/3	2,200			5	1		77	15		
5/3	2,600			2	1.5		30.5	58	8	31
7/3	3,900		3	3	6		76	12	3	
9/3	1,500			4	8	2	77	9		
10/3	2,700	1	3	6	12	3	60	13	2	
14/3	8,200	16.5	9.5	10	10	5	23	24	2	
17/3	15,000	8.5	16.5	42.5	4.5	1	22.5	5.5	2	
20/3	6,000	1	5	57	6	0.5	24	5.5	1	31
24/3	4,300		6	39	3	1	48	3		
28/3	10,200			7	8		76	9		
31/3	12,000		1	21	5	2	58	13		22
17/4	6,500	0.5	2	6	1	1	21.5	68		23
18/4	4,400			10	2		40	48		
23/4	6,000		1.5	2.5	7.5	0.5	34	52.5	1.5	26
28/4	5,800		2	1	6.5	1	46.5	41	1	

the diagnosis "angina granulocytopenica" and made a slow recovery during treatment with antibiotics. In 1953 he was operated upon for a giant cell tumour in the left humerus. There has been no sign of recurrence.

The boy was severely ill in connection with measles in 1953. Ten days after developing the disease he was taken into hospital and showed clinical and radiological evidence of bronchopneumonia and pan-sinusitis. He also had signs of laryngitis. The clinical course of this illness is shown in Fig 1 and Table 2. He had fever during the first weeks of hospital stay and had leucopenia with a pronounced neutropenia. When the temperature returned to normal, there was a transient though pronounced leucocytosis, with a marked rise in granulocytes. At the same time there was a "shift to the left" with a release of immature cells into the circulation. It can be seen from the table that the eosinophil count rose immediately before the development of the leucocytosis.

Physical examination at the age of 13 years revealed a boy who was short for his age and thin, and had an unusually small head (Fig 2). His height was 133 cm, head circumference 48.5 cm body weight 23.5 kg. He was flat-chested and had slender extremities, with long, thin, pale fingers. Valgus deformity of the feet and clumsy gait. In the skin a few scars were noted after old injuries. The gums were hyperplastic and swollen, and his breath foetid. The genitalia were small and infantile, but during the previous 6 months an increase in the size of the testicles had been noted. Mentally he showed an "old fashioned" manner. There was no evidence of splenic or hepatic enlargement nor palpable lymph nodes.

Laboratory findings

Blood group was O Rh( ). Haemoglobin level and thrombocyte counts were normal. Bleeding and clotting time normal. ESR showed moderate increase usually with values between 20–30 mm/hr. The white cell picture is illustrated in Table 1 and in relation to the clinical course during 1953 in Fig 1 and Table 2. During 1959 the white blood picture was followed in a clinically quiescent phase with counts every week for



Fig. 2. The patients L. O on the right and S.-A. O on the left.



Fig. 3. Electrophoretic curves during inactive phases.

a period of two months. No cyclical variations could be noted.

Repeated bone marrow biopsies revealed diminished myelopoiesis, mostly attributable to a reduction of mature cell types. In addition, a pronounced eosinophilia was seen, together with an increased incidence of lymphocytes and monocytes. Erythropoiesis and thrombopoesis were apparently normal

No leucocytagglutinins could be demonstrated on repeated examinations.

Serum protein examination showed a marked increase in the gamma globulin content, varying on eight occasions between 1.8 and 2.9 g% (24.9–39 7 relative %) with the median — g% (29.3 rel.). The total protein content was 7 1–7 6 g%. The increase in gamma globulins was accentuated in association with severe infections when a fall in albumin was also noted. Fig 3 shows an electrophoresis curve during an inactive phase of the disease.

Immune electrophoretic analyses have been performed on samples of blood serum. The immune globulins, γ- β_{2A} β_{2M} globulin were found in all sera and no abnormalities were detected (Lars Å. Hansson).

Amino-acid excretion in the urine was normal (R. Jagenburg).

Case 2

S A. O., born 20/7/1951 aged 10 years. The mother had rubella during the first month of pregnancy Normal delivery birth weight 2700 g Mental development followed the lower limits f the normal curve

Neutropenia was noted when he was 7 years old, in connection with a family examination in the investigation of his brother's illness. As in the case of his brother injuries led to indurated wounds resistant to healing There were similar changes in the gums dating from 6 years of age. Febrile periods had not been noted with such frequency as with the elder brother and between times he had not shown f tigue He had had several ttacks of tonsillitis.

In F bruary 1960, he had developed severe oral infection with widespread ne-

coal necroses in the throat. Fever persisted for 2 weeks and when the temperature finally returned to normal, an increase in neutrophils was noted. There was a transient enlargement of liver and spleen in connection with this episode.

On physical examination at 10 years of age, the boy was 129 cm tall, and weighed 28.5 kg, head circumference 50.5 cm. H was well-built in comparison with his brother and did not have the latter slender extremities and tapering fingers (Fig. 2). There was webbing between the 3rd and 4th digits f the hands and the 2nd and 3rd digits f the feet. Bilateral cryptorchism. The gums showed hyperplasia though less marked than in the brother There was moderate enlargement of the sub-mandibular lymph glands, but no palpable enlargement of liver or spleen.

Laboratory f nd ngs

Blood group B Rh(+). Normal values for haemoglobin and thrombocytes. Bleeding and clotting time normal. ESR showed a moderate rise. The whit cell picture is shown in T ble 3. N cyclical variation could be noted during an observation period f over 2 months.

On bone marrow examination, myelopoiesis appeared t be diminished, with reduc tion of the more mature cell forms. There was no increase in "blast" forms. Eosinophilia was noted, together with an increase in lymphocytes and monocytes.

Leucocyte agglutinins could not be demonstrated. The antistreptolysin titre was 400 units; the antistaphylolysin titre 4 units.

Serum protein electrophoresis gave total protein values varying between 6.9 and 8.3 g%; gamma globulin values from 1.3–2.5 g% (18.9–32.4 rel.%) with the median 1.8 g% (24 rel.%) As in his brother' case, the more elevated γ-globulin values were noted in connection with more severe infections, but here an increase in β-globulins was seen at the same time Fig. 3 shows the electrophoretic pattern during a quiet phase of the disease

Immune lectrophoretic analyses have been performed on samples f blood serum. The immune globulins, γ β_{2A} β_{2M}-globulin were found in all sera and no bnormalities were detected (Lars Å. Hansson).

Amino-acid excretion in the urine wa normal (R. Jagenburg)

Bone Marrow Studies

On the basis of previous studies of bone marrow function *in vitro* [22 23, 24 27] a more extensive examination of marrow function *in vitro* was carried out using the technique described by C. M. Plum [21]. (The error of the method is evaluated in ref. [27].)

Results

Case 1 (L O)

A. *Films*

These show a marked inhibition of granulocytopoiesis, and a rather pronounced eosinophilia The mature leucocytes show a marked shift to the left Erythropoiesis is also depressed apparently at the same stage of development as the inhibition of granulocytopoiesis. About 10% of cells in these films are difficult to place in well-defined cell groups.

The morphological diagnosi was severe inhibition of bone marrow function with a marked shift to the left.

B *Marrow culture experiments*

1 *Patient' own bone marrow in own serum* The bone marrow cult re wa maintained for 24 hours and from readings after 6 12 and 24 hours the rate of formation of new erythrocytes could be l culated per normoblast and hour This rate wa found to be 4.30 i.e a red ction of 18% of the a erage normal rat of

TABLE 3. *The leucocyte levels and differential counts in the younger brother S A O*

Date	White blood cells, per mm	Immature cells, %	Stab cells, %	Segmented neutrophils, %	Eosinophils, %	Basophils, %	Lymphocytes, %	Monocytes, %	Sedimentation rate
Aug 1958	3500	—		4.5	4	—	86	5.5	40
Nov 1958	5100	—	6	9	2	—	76	7	
Dec. 1958	7900	—	5	3	6	—	68	18	
Jan. 1959	4900	—	5.5	21	5	2	65.5	11	
Feb. 1960	5200	—	12	2	3	—	76	7	22
March 1960	6700	—	1.5	4.5	6	—	66.5	1.5	43
Okt. 1960	4200	—		7	4	—	74	13	23

5.39 At the same time no signs of maturation in myelopoiesis could be found.

2 *Patient's bone marrow in normal serum.* New erythrocyte formation occurred at a rate of 4.58 per normoblast and hour Plum s earlier investigations [23 27] in "crossed marrow/serum analyses have shown a reduction of about 15 % in normal individuals. In comparison, it can be said in the case in question that there is an increase in activity of about 20 %. During this experiment a slight change could be observed in the cells of the leucopoiesis, suggesting a normalisation.

3 *Normal marrow in the patient s serum.* As stated above crossed marrow/serum tests under normal circumstances show a reduction of activity of about 15 %. In the present case, normal marrow in the patient s serum produced a depression of activity amounting to 24 %.

4 No change in marrow activity could be noted following the addition of amino-acids or liver extracts to the patient s serum

Case 2 (S A O)

A. *Films*

Those largely resemble the films obtained from the brother though the inhibition of myelopoiesis seems to be somewhat less pronounced. There is no eosinophilia The number of cells which are difficult to classify with precision comprise a much greater proportion in this patient.

The morphological diagnosis was severe depression of bone marrow function, with a marked shift to the left.

B *Marrow culture experiments*

1 *Patient's own bone marrow in own serum.*

The culture was maintained for hours, being read off after 6 12 and hours to enable calculation of the rate of new erythrocyte formation, per normoblast and hour The patient s marrow in his own serum gave a figure of 4 45 compared with the normal 5.50 i.e a reduction of 17 %. No change was noted in the maturation of leucocytes.

2. *Patient s marrow in normal serum.* Here the rate of new erythrocyte formation was found to be 4 72 per normoblast hour i.e an increase of . Taking into account the fact that normal marrow and serum under these circumstances show a decreased activity of 15 %, it can be said that in this case an increase in activity of about 22 % had occurred. *At the same*

TABLE 4 *The number of leucocytes and the differential count after infusion of fresh plasma on day 1 in patient L. O*

Day	White blood cells, per mm³	Immature cells, %	Stab cells, %	Segmented neutrophils, %	Eosinophils,	Basophils, %	Monocytes, %	Lymphocytes, %
1	4600		8	7	15		39	31
2	8400		5.5	4.5	13	0 5	32.5	44
3	5000		8	7	7		26	52
4	5400		5	5	14		18	58
5	6190		3.5	6.5	14.5		23.5	52
6	4500		2	1	12	1	19	65
8	4600		6	4.5	17.5		24.5	47.5
9	4300		6	2	17		23	53
10	4800		6	4	11		26	51

time a slight increase in leucopoietic activity could be noted, viz. an increased maturation.

3 *Normal marrow in patient's serum* As stated above "crossed marrow/serum" tests normally show about 15% depressed activity In this case a depression of activity corresponding to 31% could be observed.

4 No response could be noted to the addition of amino-acids or liver extracts to the patient's serum

Transfusion Experiments

These bone marrow culture experiments showed that normal serum had a favourable effect on the bone marrow *in vitro*. We were therefore interested in discovering whether normal serum could influence the blood picture *in vivo*

Each of the brothers was given a transfusion of 400 ml fresh plasma (tapped the same day) This amounted to 14–17 ml/kg body weight The total and differential white cell counts were then checked daily on fasting The taking of samples and cell counts were carried out by the same examiner throughout Bone marrow biopsies were taken on the day of transfusion and the 5th day fter transfusion.

The results of these white cell counts in

TABLE 5. *The number of leucocyt s and the differential count after i fusion of fresh plasma on day 1 i patient S A O*

Day	White blood cells, per mm³	Immature cells, %	Stab cells, %	Segmented neutrophils,	Eosinophils,	Basophils,	Monocytes,	Lymphocytes,
1	4900		2	5	4		17	72
2	4500	0.5	2.5	5	2	5	10.5	6 5
3	5900		2	9	8		8	73
4	4400		2.5	[illegible]	3		10.5	76.5
5	4900		6	7	4		8	75
6	8100		2	3	2		8	82.5
8	7300		20	25	3		13	37.5

TABLE 6 *The myelograms before and 5 days after fresh plasma transfusion The second puncture specimen in the first patient was not perfect with an increased admixture of peripheral blood*

	Patient 1 L. O		Patient B. L. O	
	Before	5 days after transfusion	Before	5 days after transfusion
Proerythroblasts (%)	1	0.3	1.8	1.9
Erythroblasts	23.1	6.5	16.1	17.5
Myeloblasts	1 6	0 4	.3	.1
Myelocytes	4.7	14.0	19.3	20.3
Metamyelocytes + stab cells + segmented cells	15.7	49.2	19.9	35.5
Lymphocytes	22.1	23.1	24.4	13.8
Monocytes	7 1	12.7	2.1	1.9
Plasma cells	2.0	1.5	.3	2.1
Reticular cells	1 6	1 0	1.8	1.4

the older brother are shown in Table 4 No change in the peripheral blood could be observed. A true increase in the numbers of more mature granulocytes had most probably occurred in the bone marrow but this was difficult to assess on account of increased admixture of peripheral blood in the second lot of slides (Table 6) The bone marrow of the younger brother showed a significant increase of mature granulocytes and in peripheral blood a marked increase of neutrophil granulocytes was evident on the 7th day (Table 5) Unfortunately the boy developed an upper respiratory infection about the same time and could not be brought back for the purpose of further testing

Discussion

Grave neutropenia was discovered in two brothers at the age of 2 and 7 years respectively The characteristic symptoms were chronic gingivitis delayed healing of cutaneous wounds and recurring oral and pharyngeal infections These symptoms commenced early and in the case of the older brother can be traced already in early infancy Their appearance cannot be related to any particular infection or exposure to drugs. It is indeed possible that the neutropenia was present at birth or appeared shortly afterwards. The presence of constitutional anomalies strengthens the suspicion that the neutropenia is congenital. Grave chronic neutropenia is an unusual haematological finding and its existence in two brothers suggest genetic aetiology probably of recessive character

The neutropenia has remained stationary during the period of observation—11 and 3 years respectively Symptoms and blood changes appearing at intervals as in cyclic agranulocytosis have not been noted here In each case a long period of serious illness has terminated with a marked though transient rise in the neutrophil leucocyte count with an immediately preceding eosinophilia Similar observations have been made in a sporadic case of chronic granulocytopenia [19]. It would appear that the bone marrow dysfunction can be overcome temporarily in connection with serious infections

The serum protein changes are interpreted as a non-specific serological response to a more or less constant state of infection. The monocytosis in the peripheral blood is also interpreted as a compensatory reaction to decreased function of the neutrophils. Similar changes have been reported in other cases of neutropenia [13 15]

Morphologically the bone marrow is characterized by the maturation arrest" in myelopoiesis. There is also a significant degree of eosinophilia and a rise in the numbers of lymphocytes and monocytes. Erythropoiesis has usually been considered as normal, but a tendency to depression of erythropoiesis has appeared at times.

The results of bone marrow culture tests can be summarized as follows.

1 Normal bone marrow cultured in the sera of the patients did not show the same degree of activity as in foreign normal serum.

2 Both patients bone marrow showed increased activity when in culture with normal serum.

Similar observations have been made from bone marrow cultures in cases of infantile genetic agranulocytosis [25 26] and in patients with leukaemia and pernicious anaemia [4 27]. In infantile genetic agranulocytosis, the addition of cysteine to the patient s serum *in vitro* resulted in increased marrow activity and increased differentiation in the myelopoiesis [25] Administration of cysteine to th patient however orally or intravenously prod ced no demonstrable clinical effect In leukaemia, a similar increase in marrow activity was noted following the addition of cysteine and cystine to the patients sera [4] nd in pernicious anaemia tyrosine and liver extract were shown to have a similar effect on marrow cultures [27] In the two brothers studied here no effect could be noted following the addition of amino-acids or liver extract

The observations reached in the marrow culture studies can be interpreted in two ways:

1 The sera of these patients contain substances which exert a depressive effect on normal bone marrow activity

2. The patients sera are deficient in certain substances which are necessary for the maintenance of normal marrow activity

The activity of the bone marrow was assessed by means of the numbers of newly formed erythrocytes in relation to the normoblast total, so the results are not a direct picture of the stat of myelopoiesis. It is, however quite clear that the sera of the two brothers differ from normal serum as regards its effect on bone marrow *in vitro* Histologically this difference was also noted to apply in myelopoiesis

In vivo fresh normal plasma was found to have a normalizing effect on myelopoiesis in the marrow of the younger brother with a marked rise in circulating neutrophil leucocytes after 7 days which period is probably necessary for maturation of the cells. The infection which interrupted this therapeutic test can hardly have influenced the blood picture t any rat not decisively since earlier period of infection had not produced blood changes so early in the course In addition, the bone marrow hanges were noted before the outbreak of infection.

In the elder brother transfusion of plasma was not followed by leucocytosis

in the circulating blood, and neither was there any convincing effect on the bone marrow This discrepancy between the two brothers may be explained by the fact that the elder brother's illness was clinically more serious.

As aetiological explanations of this condition, the following alternatives can be considered.

1 Deficiency in the plasma of a factor essential for normal maturation in myelopoiesis.

2 The presence in the plasma of a substance (or substances) causing inhibition of myelopoiesis.

3 Primary defect of the bone marrow

The bone marrow culture experiments, and the therapeutic test of plasma transfusion in the younger brother give most support to the theory of some undetermined factor being deficient in the plasma This may be analogous with the discovery in certain cases of thrombocytopenia of a deficiency in the serum, of a factor which stimulates thrombocytopoiesis (thrombopoietin") [30]

The second alternative appears less probable bearing in mind the results of plasma transfusion However one cannot rule out the possibility that a factor capable of inhibiting myelopoiesis might be diluted by the infusion of plasma and thus rendered less active

A maturation arrest in primary bone marrow defect may be true on the basis of a defect in development at a certain stage (enzyme deficiency primary cell defect?) or apparent through an abnormally rapid disappearance of the more mature cells. The latter may be destroyed in the medulla as result of their possible abnormality Thus in a case of Fanconi's anaemia, examination with iron isotopes revealed a marked intramedullary haemolysis of red cells [31] The discrepancy between the serum of these boys, and normal serum as seen in the marrow culture experiments, cannot be explained by an isolated primary bone marrow defect, unless it might be that a brisk myelopoiesis has caused a shortage of those serum substances necessary for new formation. Morphologically however there was no sign of such a marked increase in cell formation

Comparison of these cases with other cases of chronic granulocytopenia cannot be reliable since others almost without exception, have not been examined by the methods applied in this work and, as with every disease, considerable individual variations are to be found

As regards the blood and bone marrow there are great similarities with infantile genetic agranulocytosis but the clinical course of this condition is usually much more grave usually ending fatally after a relatively short period [16] The results of bone marrow culture with the addition of cysteine also serve to distinguish this disease from our cases here

Certain cases of familial but more benign neutropenia are difficult to distinguish clinically from the present cases, but the pattern of heredity appears to be different [13 17].

The physical constitution of the elder brother short in stature with a small head and hypogenitalism (?) is the kind which can be seen in Fanconi's anaemia [40]. This disease however is practically always progressive and is fundamentally a pancytopenia so that our cases ought not to be regarded as partial Fanconi syndrome

Constitutional aberrations similar to those of our patients have also been noted in a number of cases of sporadic, chronic, granulocytopenia [7 25] These have even shown similar blood and bone marrow changes, but the course has been more favourable with a tendency to spontaneous regression. There may be some relationship between these and our own cases, but this is not conclusive

Other sporadic cases of chronic neutropenia in children have shown a clinical resemblance to infantile genetic agranulocytosis [1., 16 18]. Other cases again have shown only moderate neutropenia and a benign course without fundamental similarities to our two cases [8 20 22, 24].

Summary

Two brothers with familial neutropenia are reported. They have had symptoms of their disease since early infancy A pronounced neutropenia has been a continuous finding in the peripheral blood. Serum electrophoresis has shown a reactive hypergammaglobulinaemia. A maturation arrest at the myelocyte level is seen in the bone marrow *In vitro* bone marrow culture experiments from these two brothers showed that their serum did not permit the same growth activity of bone marrow as normal serum. Transfusion of fresh plasma to the brothers led to a short time normalization of myelopoiesis in one brother and a doubtful effect in the other It is suggested that the hereditary defect in these two brothers may express itself in a deficiency in serum of a factor necessary for normal myelopoiesis.

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Department of Pædiatrics
Barnsjukhuset
Göteborg SV
Sweden

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From the Department of Bacteriology and the Department f Pædiatrics,
University of Gothenburg Sweden

A Comparison of the Antigenic Relationships of Human Milk and Goat s Milk to Bovine Milk

by LARS Å. HANSON AND H J ANDERSEN

In the dietary treatment of infants with cow s milk allergy goat s milk has often been tried with varying results [4, 16, 17]. In a recent report an antigenic relation ship between goat s and cow s milk has been demonstrated by means of diffusion in-gel methods [3]. These authors assume that this relationship makes goat s milk an unsuitable diet for patients with aller gies to cow s milk. Saperstein [15] has come to similar conclusion by means of precipi tin and anaphylactic tests, using rabbit immune sera against α-lactalbumin and β-lactoglobulin.

Human milk can usually be given with good results to children with allergic reactions to bovine milk. For this reason we wanted to compare the antigenic rela tionship between bovine and human milk and the relationship between bovine and goat s milk.

Material

Antigens Fresh unpasteurized cow and goat s milk were employed well as human milk taken 2 3 weeks after parturition. Merthiolate was added to a concentration of 1/10,000.

Immune sera. Anti-bovine colostrum sera were prepared in rabbits by weekly injections of ml of bovine colostrum for 4 weeks. The fifth week they were bled. One week after monthly booster doses additional bleedings were obtained.

In identification experiments anti-bovine blood serum, anti-human blood serum and anti human milk immune sera were also utilized.

Method

The studies were ccomplished by means of the immune electrophoretic method of Grabar & Williams [5, 6] in the modification described by Wadsworth & Hanson [18].

Results

Immune electrophoretic analyses of bovine milk with anti-bovine colostrum serum shows a spectrum consisting of 12 precipitation lines (Fig 1) Several of these precipitates have been designated by means of comparative studies with bovine milk fractions and bovine blood serum [8 10 11]. As indicated in the figure lines have been referred to α lactalbumin, se rum albumin, β-lactoglobulin red protein, casein and an immune globulin compo nent.

Analyses of human milk with anti bo vine milk immune serum shows a precip itation spectrum of four lines (Fig *) By means of anti-bovine or human blood

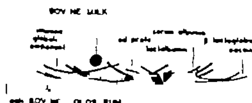


Fig 1 Immune electrophoretic analysis of bovine milk by means of an anti-colostrum serum. Identified precipitates are indicated.



Fig 2 Immune electrophoretic analysis of human milk by means of an anti bovine colostrum serum. Identified precipitates are indicated.

serum immune sera two of these precipitates can be related to serum albumin and γ-globulin. The precipitate formed by a substance related to serum γ-globulin is indicated immune globulin component (Fig 2) The most dense precipitate is identified as formed by α lactalbumin.

Goat s milk studied by means of anti bovine colostrum serum shows a spectrum of three precipitates (Fig 3) Using the anti-bovine blood serum one of these precipitates can be referred to serum albumin, whereas another indicated immune globulin component is related to serum γ-globulin. The third precipitate is formed *by a substance related to bovine α lactalbumin*. The latter precipitate showed a splitting of its anodic end in some experiments.

Discussion

From our studies it is evident that there exists an antigenic relationship between serum albumin α lactalbumin and an immune globulin component in goat s and cow s milk (Fig 3) It is also evident, however that there is a similar relationship between the corresponding proteins in human and bovine milk. A relationship is also demonstrated for an additional protein in human and bovine milk (Fig. ?).

The fact that practically every case of cow s milk allergy in infants may be given human milk without any complications may indicate that the aforementioned *findings have no direct application* to the allergic reaction of a patient sensitive to cow s milk. A similar relationship was

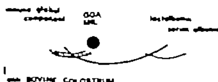


Fig 3. Immune electrophoretic analysis of goat milk by means of an anti-bovine colostrum serum. Identified precipitates are indicated.

found between proteins in cow's and goat's milk by Crawford & Grogan [3] and they inferred that goat's milk cannot be given to infants with cow's milk allergy. Augustin [ ] has criticized the use of sera from hyperimmunized animals in diffusion-in-gel methods to study allergens. The antigenic properties demonstrated in that way may have no bearing upon their allergenicity. Our findings seem to indicate that antigenic relationships as revealed by hyperimmune sera from animals in diffusion-in-gel methods may not be assumed to demonstrate any allergenicity of substances antigenically related to known allergens, for example for goat milk proteins in the patient with a cow's milk allergy.

Several authors have reported difficulties in demonstrating antibodies to known allergens in sera from allergic patients by means of diffusion-in-gel methods [1, 13]. In this connection it may be of interest to note that in some cases of cow's milk allergy in infants antibodies against milk proteins have been demonstrated by a double diffusion-in-gel method [9]. The importance of these antibodies for the allergy in the patient is not clear, however, as antibodies against bovine milk proteins have been demonstrated in a large number of healthy infants by means of a haemagglutination technique (7).

From a clinical point of view it has been found that patients with eczema and positive cutaneous reaction to cow's milk usually are not improved on goat's milk [12], while patients with gastro-intestinal reactions or severe anaphylactic manifestations usually tolerate goat's milk well [4, 12]. Reactions to human milk are reported only in a few cases [14].

Summary

1. By means of diffusion-in-gel methods a similar antigenic relationship has been found between bovine and human milk as between bovine and goat's milk.

2. From clinical work it is well-known that human milk, but not always goat's milk, is tolerated by patients with cow's milk allergy. Thus it seems probable that the demonstrated antigenic relationships have no bearing on the allergic reaction in the cow milk-sensitive patient.

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The skilful technical assistance of Mrs. Anita Larsson is appreciated.

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Paediatric Clinic
Barnsjukhuset
Gothenburg
Sweden

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From the Department of Physiology (Head: Professor Kaarlo Hartiala, M.D.) and from the Pediatric Clinic (Head: Professor Toivo Salmi, M.D.), University of Turku, Turku, Finland

The Development of the Nitrogen Content of Human Organs in Early Fetal Life

I Glandular Organs

by MARTTI PULKKINEN HEIKKI A. SALMI and PETTER SAVOLA

The fetus takes the nitrogen it needs from the mother's blood. According to Huggett [5] a child on account of increased protein synthesis, has a large store of protein, especially in the last months of pregnancy and about the time of birth. The protein is chiefly in muscle and in liver. At the time of birth the amount of fetal nitrogen is 55–60 g. The placenta has been said to play an important part in the protein balance of the fetus. It probably synthetizes new protein for the fetus out of the material it takes from the mother. This protein differs both in the amount and in the quality from that of the mother's blood. The protein content in fetal serum increases continually during pregnancy. The originally rather high store of albumin falls to normal values about the time of birth. γ-globulins increase during the earlier stage of pregnancy so that they are twofold compared with the mother's corresponding concentration. α- and β-globulins increase only to subnormal values [1–4].

The purpose of this study was to describe the total nitrogen content of each organ during early pregnancy. The purpose was further to try and answer the question, where is this largely available nitrogen to be found in the fetus? The authors also wished to make comparative studies of the amount of nitrogen per unit of weight in different organs.

Material and Method

The material consisted of 60 fetuses, the length of which varied from 2.5 cm to 28.5 cm. The collecting of material and the preparing of the organs has been described in previous study [6].

The nitrogen determinations have been carried out using tissue homogenates made in distilled water with the Potter Elvehjem glass homogenizer [7]. The nitrogen was assayed by the micro-Kjeldahl method. K_2SO_4 and $CuSO_4$ were used during the evaporation of the water with the addition of occasionally 30 % hydrogen peroxide. The ammonia was distilled in boric acid and titrated with sulphuric acid to the colour-change point of bromcresol green — methyl red mixture as indicator. One millilitre of consumed 0.01 N sulphuric acid corresponded to 0.14 mg N. This method was accurate to 0.1 1.0 mg N.

TABLE 1 *Organ nitrogen concentration in human fetuses*

Tissue	Number of determinations	Concentration, mg/g wet weight	
		Mean $\pm s(\bar{x})$	$s(x)$
Parotid gland	25	10.4 ± 0.96	4.8
Thyroid gland	39	14.7 ± 0.79	4.8
Thymus	40	15.8 ± 0.82	5.2
Pancreas	38	13.4 ± 0.73	4.5
Adrenal gland	54	12.0 ± 0.58	4.2

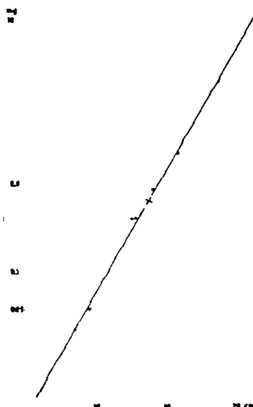


Fig 1 The regression of the nitrogen content of the parotid gland in regard t the crown heel length of the fetus.

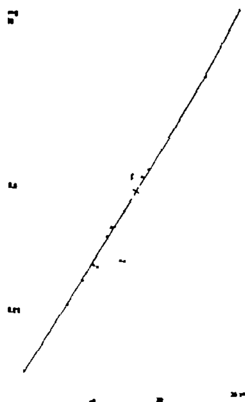


Fig — The regression of the nitrogen content of the thyroid gland in regard to the crown-heel length of the fetus.

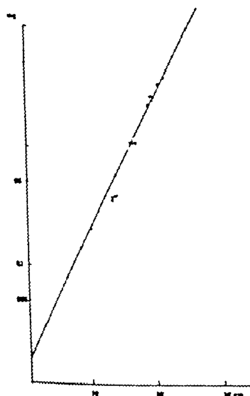


Fig. 3. The regression of the nitrogen content of the thymus in regard to the crown–heel length of the fetus.

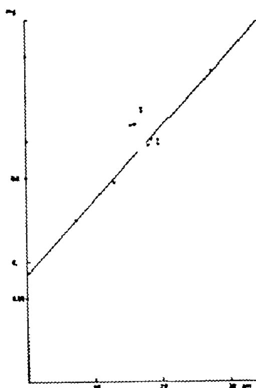


Fig. 4. The regression of the nitrogen content of the pancreas in regard to the crown–heel length of the fetus.

Results

The results are given in Tables I and 2 and in Figs. 1–5.

Discussion

The growth of the total nitrogen content should be greater than the growth in the weight of the organ during the same time because it is known that the water content of the fetus falls as it grows older [6], the same tendency of development that is typical of the developing organism during the postnatal period. The water content of the fetus falls from 93% to 4 during the fetal phase when passing from the 2nd month to the 10th month. If one compares the results of the total nitrogen determinations in this study with those previously presented on the weights of the organs [8] one observes that the rise of the nitrogen content is greater than the rise in the fresh weight of the tissue.

The thymus has the highest nitrogen content of all of the glands. The production of lymphocytes and the storing of proteins has been generally regarded as a function of the thymus. The present study supports this concept. A high nitrogen content may be caused either by a high protein content or a low water content or by both. It is known that the thymus is

TABLE * *Total organ nitrogen content in human fetuses*

Tissue	Number of fetuses	Length of fetuses, cm Range	Length of fetuses, cm Mean	s(x)	Mean nitrogen content, mg	Increase of total nitrogen content, log mg N/cm	
Parotid gland	_5	8.5 − 28.5	17.0 ± 1.08	5.3	0.38 ± 0.00	0.092 ∓ 0.033	0.441
Thyroid gland	38	10.0 − 28.5	16.2 ± 0 75	4 6	0.45 ± 0.0˜	0.091 ∓ 0 019	0.904
Thymus	40	8.0 − 28.5	16.3 ± 0 90	5.4	1 01 ± 0.22	0.111 ∓ 0.024	0.914
Pancreas	38	9 0 − 28.5	17.3 ± 0.73	4.4	0.91 ± 0.14	0.062 ∓ 0.038	0.631
Adrenal gland	54	3.5 − 28.5	14.4 ± 0.81	5.8	1 15 ± 0.31	0.097 ∓ 0.017	0.903

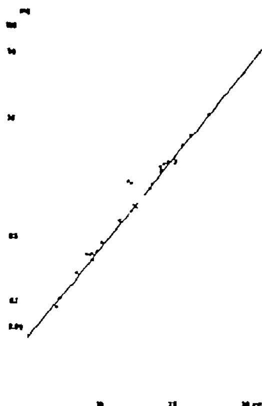


Fig 5. The regression of the nitrogen content of the adrenal gland in regard t the crown–heel length of the fetus.

an active organ in a growing organism before the maturation of the sex glands. One might expect a large amount of nitrogen in active glandular tissue. The parotid gland contains the smallest amounts of nitrogen. If nitrogen content is directly related to function, the parotid gland is probably in a state of rest

Summary

The nitrogen content of adrenal gland, parotid gland, thyroid gland, thymus and pancreas was determined in 60 human fetuses, the length of which varied from ?.5 cm to 28.5 cm. The nitrogen content per unit of weight of the gland examined was determined. The thymus contained the largest and the parotid gland the smallest concentrations of nitrogen. The largest total contents of nitrogen were found in the adrenal gland and the smallest in the parotid gland

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Pediatric Clinic
University of Turku
Turku
Finland

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From the Department of Physiology (Head Professor Kaarlo Hartiala, M D) and from the Pediatric Clinic (Head. Professor Toivo Salmi, M.D) University of Turku, Turku, Finland

The Development of the Nitrogen Content of Human Organs in Early Fetal Life

II Non Glandular Organs

by HEIKKI A. SALMI MARTTI PULKKINEN and PETTER SAVOLA

In a previous work [3] the authors studied the development of the nitrogen content of glandular tissues of the human fetus during early pregnancy This article reports the results from the other tissues, and is also concerned with the comparison of nitrogen content of various fetal tissues.

Material and Methods

The source of tissue was 57 human fetuses, the length of which varied from 2.5 cm t 28.5 cm. The gathering of material, the hand ling of it, the technique of nitrogen determi nation and the statistical methods have been described previously [3, 4].

Results

The results are given in Tables 1 and 2 and Figs 1–8.

Discussion

The total organ nitrogen content in the fetus was greatest in the brain and liver Total brain content was twice that of the liver The nitrogen concentration was greatest in the spleen. This high content may be related to the active hematopoiesis of the fetal spleen. The second highest concentration was in the liver which in the fetus has some of the same functions as the

TABLE 1 *Organ nitrogen concentration in human fetuses*

Tissue	No. of deter mina tions	Concentration, mg/g wet weight	
		Mean ± s(x̄)	s(x)
Liver	57	18.0 ± 0 79	5.5
Kidney	57	11 8 ± 0.35	2.6
Stomach	47	10.8 ± 1.04	7 1
Alimentary tract	11	14.2 ± 1.94	6.6
Heart	44	1_.6 ± 1.50	9.9
Lung	51	9.8 ± 1.34	9 6
Brain	54	11.6 ± 0.77	5.3
Spleen	35	"0.2 ± 0.92	5.4

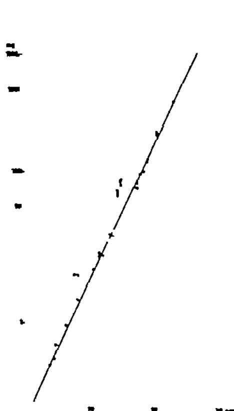


Fig. 1. The regression of the nitrogen content of the liver in regard to the crown–heel length of the fetus.

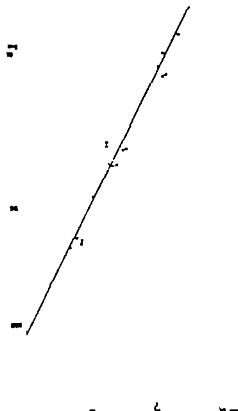


Fig. 2. The regression of the nitrogen content of the kidney in regard to the crown–heel length of the fetus.

TABLE 2. *Total organ nitrogen content in human fetuses*

Tissue	Number of fetuses	Length of fetus, cm			Mean nitrogen content, mg	Increase of total nitrogen content, log mg N/cm	
		Range	Mean	$s(x)$			
Liver	53	3.9–28.5	13.8 ± 0.88	6.3	20.0 ± 1.37	0.113 ∓ 0.018	0.895
Kidney	57	2.5–28.5	13.6 ± 0.90	6.0	1.18 ± 0.23	0.109 ∓ 0.012	0.906
Stomach	45	4.8–28.5	14.7 ± 0.77	5.3	0.959 ± 0.159	0.067 ∓ 0.018	0.884
Alimentary tract.	11	2.5–11.0	6.3 ± 0.63	2.2	1.00 ± 0.53	0.199 ∓ 0.016	0.790
Heart	45	4.0–28.5	13.6 ± 0.95	6.2	2.5 ± 0.49	0.094 ∓ 0.016	0.925
Lung	47	3.8–28.5	13.8 ± 0.88	6.0	13.6 ± 2.8	0.089 ∓ 0.019	0.909
Brain	51	2.8–28.5	13.3 ± 0.08	6.3	58.2 ± 8.8	0.070 ∓ 0.010	0.942
Spleen	34	9.0–28.5	17.4 ± 0.84	4.7	0.960 ± 0.77	0.091 ∓ 0.003	0.845

The entire alimentary tract, including stomach, was included in fetuses < 11.0 cm.

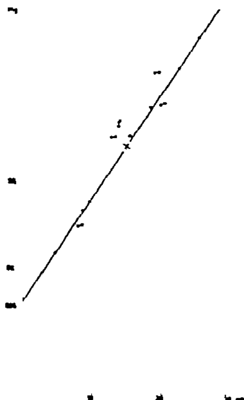


Fig. 3. The regression of the nitrogen content of the stomach in regard t the crown–heel length of the fetus.



Fig. 5. The regression of the nitrogen content of the heart in regard t the crown–heel length of the fetus.

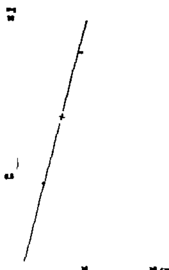


Fig. 4 The regression of the nitrogen content of the alimentary tract in regard to the crown–heel length of the fetus.

spleen. Comparison with a previous report [4] shows that the thymus, which is also a particularly active organ in the fetus, was next in order of concentration. The lung parotid gland [4] and brain had the lowest nitrogen concentrations. The lung and parotid gland are inactive tissues in the fetus. The cerebral cortex is also inactive until late in fetal life as shown by the study of the EEG of the fetal lamb [1]. Myelination of nerve tracts i also late in development The water in the brain is high during fetal life and decreases markedly during postnatal development The increase in fat content of tissues during fetal life which does not continue in the

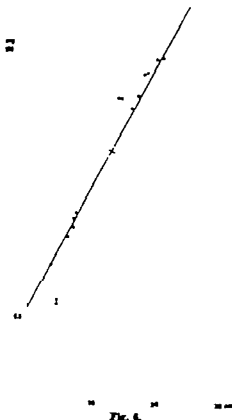


Fig. 6.

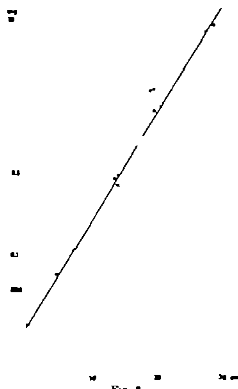
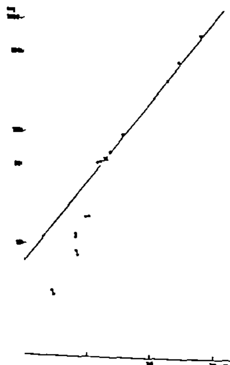


Fig. 8.

Fig. 6. The regression of the nitrogen content of the lung in regard to the crown–heel length of the fetus.

Fig. 8. The regression of the nitrogen content of the spleen in regard to the crown–heel length of the fetus.



postnatal period [2], must influence the nitrogen and protein concentration.

Summary

The nitrogen content of 57 human fetuses, the length of which varied from 2.5 cm to 28.5 cm, was determined in eight different organs, viz. liver, kidney, stomach, alimentary tract, heart, lung, brain, and spleen.

The nitrogen content per weight unit of these organs was also measured. The spleen and the liver contained the largest

Fig. The regression of the nitrogen content of the brain in regard to the crown–heel length of the fetus.

concentrations of nitrogen, the lung and the brain the least. The largest total contents of nitrogen were found in the brain and liver the smallest in the stomach and spleen.

The regression of the total nitrogen content in regard to the length of the fetus varied from log 0.070 mg N/cm to log 0.190 mg N/cm.

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Pediatric Clinic
University of Turku
Turku
Finland

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From the Department of Pediatrics, University of Gothenburg, Gothenburg, Sweden

Plasma Transfusion Treatment of Six Children with Idiopathic Thrombocytopenic Purpura

by GUNILLA BERGLUND

Introduction

The treatment of idiopathic thrombocytopenic purpura (ITP) must be based on clinical experience as long as the etiology is obscure. The present conception that ITP is a condition caused by an immunological reaction does not solve the problem of treatment as long as the cause of the antibody production against the platelets is unknown. The commonly used treatment in ITP cortisone and splenectomy is beneficial in about 80–85 % of the patients. Both of these treatments have some side effects and risks. In 1950 Schulmann *et al.* [2] demonstrated that plasma transfusions could be efficacious in the treatment of an 8-year-old girl with ITP. Though no effect was obtained after treatment with cortisone or by splenectomy remissions of a month duration were achieved after each of many transfusions of fresh frozen plasma. They credited this effect to a plasma factor increasing the number of platelets. On the basis of this report plasma transfusions were introduced as the initial treatment of all ITP cases, which have been hospitalized at the Children's Hospital Göteborg, since May 1st 1960.

This report concerns six patients with ITP who received fresh plasma transfusions

Case Histories

Case E. H. (Fig. 1). A 14-month-old girl without any known heredity for bleeding disorders was admitted because of a bleeding tendency with mucosal bleedings, hematomas and petechiae since 2 months of age. On admission the girl was in good condition except for hematomas of different ages scattered over the body and a fair amount of petechiae on the upper part of the body. The tourniquet test was positive. The laboratory investigations showed ESR 4 mm/hour, Hgb 12.4 g%, WBC 8,100 mm³, platelets 3,000 mm³, bleeding time 16 minutes, clotting time 6 minutes, prothrombin index 120. The bone marrow smear showed a normal picture. During the first 12 days in the hospital, when no treatment was given, the platelets varied between 3,000 and 15,000 mm³. Thereafter a transfusion of 20 ml fresh plasma/kg body weight was given. The platelets increased and reached a maximum value of 254 000/mm³ on the 8th day. The bleeding time was 1 min. t. 30 sec. Within the next few days the platelet count had diminished to around 150,000/mm. During the subsequent observation time of about 18 months the platelets remained unchanged between 150,000 and 200,000 mm. The bleeding time was normal and the patient had no bleeding manifestations.

Case A. K. (Fig. 2). A 5-year-old girl, previously healthy and without any known bleeding disorders in the family was admitted because of a bleeding tendency with mucosal bleedings, hematomas and pete-

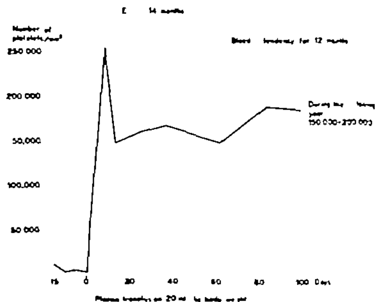


Fig. 1 Case E.H.

chiae during the 3 months prior to admission. On admission she was tired and pale, covered with petechiae and hematomas of different ages. She was also bleeding from the tonsils. Otherwise nothing relevant was found at the physical examination The tourniquet test was positive. The laboratory investigations showed ESR 4 mm/hour Hgb 10.6 g%, WBC 8,700 mm platelets 11,000 mm bleeding time more than 30 minutes, clotting

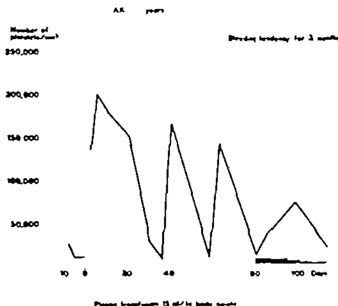


Fig 2. Case A.K.

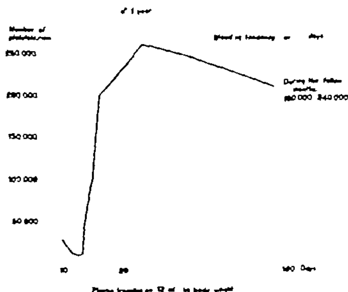


Fig. 3. Case L.A.

time 5 minutes, prothrombin index 93. The bone marrow smear showed a slight increase of the thrombocytopoiesis with an in creased number of megacaryocytes, and particularly of the more immature forms. After week of observation when the laboratory results remained unchanged the patient was given a transfusion of 15 ml fresh plasma/kg body weight. A gradual increase of the platelets was noted with the maximum value of around 200 000/mm³ on the 8th day and thereafter the platelet count was above 150,000 mm for about 20 days. During this time she did not have any bleeding manifestations, the bleeding time was normal and the bone marrow normalized. On the 33th day after the transfusion the platelet count had fallen t its original value and a second plasma transf sion of the same quantity was given. The patient had another remission, this time with a somewhat lower maximum value of the platelets, 165,000 mm and of only 20 days duration. Then third plasma transfusion was gi en. This time the platelets reached a level of 145,000/mm and the duration was somewhat shorter than after the second transfusion. The plasma transfusions were not repeated, and the patient was given prednisolon (2.5 mg/kg body weight). After an initial slight increase the platelet count diminished again. Though the bleeding time was prolonged, the bleeding manifestations seemed to have diminished.

Case L. A. (Fig. 3). This 18-month-old, previously healthy boy was admitted because of a bleeding tendency the week before admission. The patient had not shown any signs of infection before or during this time. On admission he was in good general health. H had scattered hematomas on the face and on the legs and petechiae on the face and abdomen. The remainder of the physical examination was unremarkable. The laboratory investigations showed ESR 6 mm hour Hgb 11 6 g%, WBC 8,900/mm platelets 30,000 mm bleeding time more than 30 minutes, lotting time 6 minutes and prothrombin index 74. The tourniquet test was positive. The bone marrow smear wa normal. During the following 10 days the bleeding time remained unchanged and the platelets varied between 8,000 and 30 000 mm During this time no treatment was given.

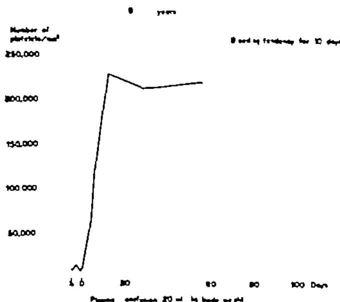


Fig 4 Case A.B.

Thereafter 12 ml fresh plasma/kg body weight was transfused. The platelets increased during the following 10 days to above 200,000/mm and the bleeding time was normal. Thereafter the platelets remained normal during the 7 months of observation and no bleeding manifestations occurred.

Case A B (Fig 4) An 8-year-old girl, previously healthy and without any known bleeding disorders in the family was hospitalized because of a bleeding tendency with hematomas and petechiae during the 5 days prior to admission. The patient had not shown any signs of infection before or during this time On admission she was in good general condition and except for hematomas all over the body and petechiae on the upper part of the body *the physical examination* did not reveal anything remarkable The tourniquet test was positive The laboratory investigations showed ESR 3 mm hour Hgb 11.8 g% WBC 7,800 mm platelets 6,000 mm bleeding time more than 20 minutes, clotting time 7 minutes, prothrombin index 92. The bone marrow smear showed a normal picture During the first 5 days in the hospital no treatment was given, *the platelets* varied between 6,000 and 12,000/mm and the bleeding time was above 20 minutes. A transfusion of 20 ml fresh plasma/kg body weight was given. There was an increase of the platelet amount which reached values above 200,000/mm on the *10th day after* the transfusion and the bleeding time normalized. During the observation time of months the platelets and the bleeding time stayed normal and the patient did not have any bleeding manifestations.

Case S P A 5-year-old adopted boy whose hereditary background was unknown, was hospitalized because of *bleeding manifestations* since the age of 1 year H bruised easily and often developed hematomas At the physical examination on admission *status of good health* was revealed except for many hematomas all over the body The tourniquet test was positive The laboratory investigations bowed ESR 3 mm hour Hgb 13.5 g % WBC 6 000 mm platelet 40,000/mm bleeding time 8 minutes 30 seconds, clotting time 6 minutes, prothrombin index 11 % LE-cell were *found*. The bone marrow smear showed slight decrease *in the number of megacaryocytes*. After 13

days of observation with unchanged laboratory values he was given a transfusion of 12 ml fresh plasma/kg body weight. An increase of the platelets to 70,000/mm³ was achieved on the 4th day but the platelet number diminished again. A second transfusion of 18 ml fresh plasma/kg body weight was given 6 days after the first. No significant changes in the platelet values were obtained after that transfusion. Treatment with prednisolone (2 mg/kg body weight) was instituted. An initial increase of the platelets to values around 150 000/mm was observed, but after a few weeks the count stabilized at around 70,000/mm³ where it remained after the prednisolone was discontinued. In spite of this fairly low platelet count the patient no longer showed bleeding manifestations.

Case I. M. This 10-year-old girl was admitted from another hospital because of a bleeding tendency with hematomas and mucosal bleedings since the age of 2 years. She had earlier been treated with blood transfusions a few times because of blood loss, and also with prednisolone (1 mg/kg body weight) at three instances, each time with a beneficial effect of short duration. She did not have a hereditary history of bleeding manifestations although it was found that both her father and brother had platelet values around 150,000 mm. On admission she was in good condition, and, except for hematomas on the legs and bleedings from the left tonsil, nothing relevant was found at the physical examination. The tourniquet test was positive. The laboratory investigations showed ESR 7 mm/hour, Hgb 1..9 g%, WBC 4 600/mm³, platelets 40,000 mm³, bleeding time 6 minutes 30 seconds, clotting time 4 minutes, prothrombin index 85, antihemophilic factor content 94 %. The bone marrow smear showed a normal picture. During the first 7 days in the hospital, when no treatment was given, the platelets varied between 22,000 and 56,000 mm³. Thereafter a transfusion of 10 ml fresh plasma/kg body weight was given. No significant change of the platelet count was obtained. A second transfusion of 20 ml fresh plasma/kg body weight was then given 10 days later. Again no change in the platelet count was achieved. Therefore a splenectomy was performed. During the following week a gradual increase of the platelets up to values around 200 000/mm was noted and this value has been maintained throughout an observation time of a month.

Discussion

Of the six patients treated with fresh plasma transfusions four responded with a normalization of the platelet count and bleeding time. Three of these have remained normal for observation periods of 2–14 months duration. In the fourth patient a remission of about a month's duration was achieved after each of the three transfusions. Two patients did not respond to the transfusions.

It seems doubtful that the rise in the platelet count in the four responding patients was due to coincidental spontaneous remissions. Of the three with complete remissions two had a short history of the disease and in each of these two the plasma transfusion might have caused a remission of limited time and during this time the disease may have undergone spontaneous recovery. The third case however had a history of the disease of 13 months and it would appear very unlikely that a spontaneous remission would occur just at the time of treatment or during the following month. That the fresh plasma really had an effect on the number of platelets is clearly shown in Case A.h., the patient receiving three transfusions (Fig.). This action cannot be explained by the effect of the transfused platelets because the number of undamaged transfused platelets must have been sparse

since the transfusions were given with ordinary glass bottles and needles. In addition it is known that the survival time of the platelets is 8–10 days [1] so probably no transfused platelets were still surviving when the maximal effect of the plasma transfusions was achieved usually after 8–10 days. The effect of the plasma transfusion might be explained by a platelet stimulating factor as suggested by Schulmann *et al* [2] but the permanency of the results in Case E.H. could only be explained by a definite change in the patient due to the plasma either inducing the formation of the platelet stimulating factor in the patient herself or by changing her immunological response. The presence of a platelet stimulating factor in plasma is supported by the response in a hemophilic patient [personal observation]. Prior to the transfusion of 20 ml fresh plasma/kg body weight the patient had a platelet value of 256 000/mm³ however between the 6th and 10th day after the transfusion a platelet value of 800,000/mm³ was attained. This is in accord with Schulmann *et al* [3] who claim the presence of a platelet stimulating factor in plasma based on the results of experiments with rats and findings in patients with ITP. The idea that a large plasma transfusion could effect the immunological mechanism might be worth some consideration as a working hypothesis. This may be supported by the fact that in some other autoimmune diseases such as colitis ulcerosa and multiple sclerosis, remissions can also be induced by large transfusions of plasma or blood. The 2 patients who did not respond despite a second transfusion were the ones with the most prolonged histories of ITP and perhaps the plasma cannot be effective so many years after onset of the disease.

Summary

Six patients with ITP have been treated with fresh plasma transfusions, 10–40 ml/kg body weight. Of these four showed remissions, one of only a month's duration after each of three transfusions, the remissions of the other three were permanent. Two patients did not respond to the transfusions. The beneficial effect attained might be due to a stimulation of the platelet formation by a factor in the plasma or possibly to a change in the immunological mechanism.

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Department of Pediatrics
Barnsjukhuset
Göteborg
Sweden

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From the Department of Pediatrics, Karolinska Sjukhuset Stockholm

Respiratory Studies in Children X

Lung Volumes in Relation to Ventilatory Capacity and Mechanical Properties of the Lungs in Symptomfree Asthmatic Children

by INGA ENGSTRÖM and PETTER KARLBERG

Hyperinflation and decreased ventilatory capacity in asthmatic children during clinically symptom-free periods have been reported separately in several studies [1 2 14, 15 22, 25]. The question has been raised as to whether the hyperinflation found is of functional origin due to bronchial obstruction or if it may be a reflection of emphysema with loss of elasticity of the lung parenchyma [1 3 22, 23 4]. The investigation performed by Kraepelien showing a decrease of hyperinflation after bronchodilator therapy has emphasized a *functional* component of hyperinflation [23] This study however gives only indirect evidence of bronchial obstruction. Direct measurement of bronchial obstruction can be obtained by measuring the pulmonary flow resistance [7 8 12, *7 *9] It is also possible to get an understanding of a change in the elastic properties of the lungs by measurement of the lung compliance [* 8 1* *7 29 30]. These two standards in conjunction with the measurement of the lung volumes and the ventilatory capacity as reflected in timed vital capacity may give further aid in analyzing the mechanisms of respiratory dysfunction in asthmatic children. The present study gives these data obtained at the same session and the relationships between different measures.

Material

Fifty-one asthmatic children between the ages 7 and 16 years, *6 boys and 25 girls, were studied. The physical development of the children was estimated by relating height to age and weight to height [5]. The majority of the children were uniformly distributed between 2 standard deviation limits for healthy children for these relationships. Three children fell just outside 2 SD for height to age one below and 2 above One child was above SD for weight to height and 3 just below 2 SD for the same relationship. The children were selected from the allergy outpatient departments and the allergy wards at the Pediatric department of Karolinska Sjukhuset and the Sachs Children Hospital, Stockholm.

Forty-four of the children were studied during period free from asthmatic symptoms as judged from physical examination and history and were without symptomatic treatment [**]. The severity of the disease was estimated as in previous studies from

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this laboratory according to the frequency of asthma attacks during the last year:

Group I—less than 5 attacks a year
Group II—5 to 10 attacks a year
Group III—more than 10 attacks a year or prolonged status asthmaticus.

However, as in previous studies [22] no difference regarding lung volumes was found between Groups I and II, the children in this study therefore have been differentiated in only two groups:

Group I + II— 6 children,
Group III —18 children.

The 7 additional children were in a more labile state with occasional ronchi and some were on symptomatic treatment. They were all assigned to Group III.

Methods with random error of the methods

The asthmatic children in this study were investigated during the same study period as the healthy children previously reported [16]. The same methods and the same procedure were applied. The mechanics of breathing were obtained by simultaneous recording of intraesophageal pressure changes and respiratory volume changes via a "reverse plethysmograph" system previously described [16]. The lung volumes were measured by spirometry and the closed circuit helium dilution technique and the timed vital capacity by spirometry with a fast moving kymograph. For further details reference is made to Respiratory Studies in Children IX [16]. Calculations of the random error of the methods gives a coefficient of variation for lung compliance of 7.. % and for pulmonary flow resistance of 12.8 %, thus of the same magnitude as in healthy children. No statistically significant difference is found between duplicate determinations of lung volumes in contrast to healthy children [16]. The coefficients of variation for vital capacity both two-stage and forced one-stage are somewhat higher than in healthy children indicating a greater instability in the asthmatic children, 47 % and 1.54 % respectively compared with 1.29 % and 0.74 in healthy children.

Results

All values are plotted versus height on double logarithmic scales in Figs. 1–. Regression calculations according to Snede

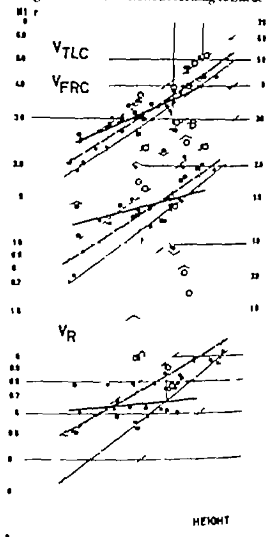


Fig. 1. Total lung capacity (V_{TLC}), functional residual capacity (V_{FRC}) and residual volume (V_R) in relation to body height on double logarithmic plot.

Group I + II symptom-free asthmatic children
Group III
○ Not quite symptom-free asthmatic children.

Regression line for healthy children with 95 % confidence interval.

Regression line for Group I + II.

Regression line for Group III

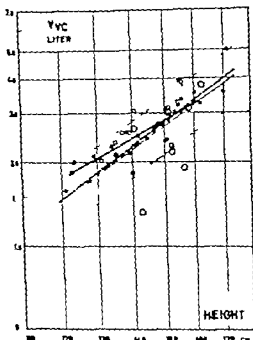


Fig. [illegible] Vital capacity (V_{VC}) in relation to body height on double logarithmic plot.
Group I + II, Group III symptom-free asthmatic children
○ Not quite symptom-free asthmatic children.
Regression line for healthy children with 95 % confidence interval.
Regression line for Group I + II.
Regression line for Group III.

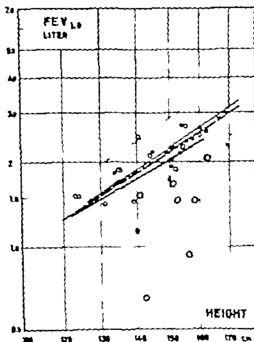


Fig. 3. Forced expiratory volume during one second ($FEV_{1.0}$) in relation to body height on double logarithmic plot.
Group I + II, Group III symptom-free asthmatic children
○ Not quite symptom-free asthmatic children.
Regression line for healthy children with 95 % confidence interval.
Regression line for Group I + II.
Regression line for Group III.

cox [33] have been performed for the two groups of symptom-free asthmatic children and the obtained regression lines are drawn in the figures. The regression lines for healthy children with their 95 % confidence intervals are also indicated [16]. The 7 not quite symptom free children are marked separately and not included in the calculations.

Deviations of the regression lines for asthmatic children from those of healthy children are visible in the charts. The significance of these differences has been tested by analysis of covariance regarding distance as well as slope [33] (Table 1). In *Group I + II* the regression lines of residual volume (V_R), functional residual capacity (V_{FRC}) and total lung capacity (V_{TLC}) are statistically significantly higher than in healthy children. The regression lines of two-stage vital capacity (V_{VC}), forced expiratory volume during one second ($FEV_{1.0}$), dynamic lung compliance and pulmonary flow resistance, however, do not differ significantly from those of healthy children with respect to distance

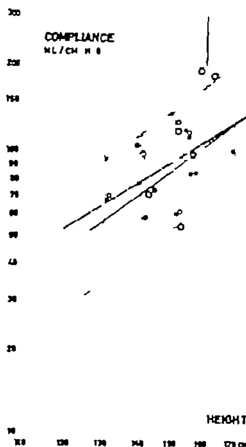


Fig. 4. Lung compliance in relation to body height on double logarithmic plot.
Group I + II
Group III symptom free asthmatic children.
○ Not quite symptom free asthmatic children.
} Regression line for healthy children with 95 % confidence interval.
— — — Regression line for Group I + II
——— Regression line for Group III

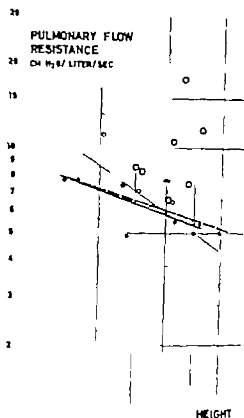


Fig. 5. Pulmonary flow resistance in relation to body height on double logarithmic plot.
Group I + II
Group III symptom free asthmatic children.
○ Not quite symptom-free asthmatic children.
} Regression line for healthy children with 95 % confidence interval.
— — — Regression line for Group I + II.
——— Regression line for Group III.

A significant difference in slope is found only for residual volume and pulmonary flow resistance. In *Group III* the regression lines of residual volume, functional residual capacity, total lung capacity, vital capacity and dynamic lung compliance are statistically significantly higher than in healthy children. With the exception of vital capacity these regression lines are also statistically significantly different in slope from those of healthy children. The regression line of forced expiratory volume during one second is statistically significantly lower than in healthy children but does not differ in slope. Only the regression line for pulmonary flow resistance in *Group III* does not show any significant difference in relation to that of healthy children.

The correlation coefficient for the dif

TABLE 1 *Analysis of covariance between the regression lines found for symptom free asthmatic children and for healthy children*

	Difference between slopes	Difference between distances
	Group I + II versus healthy children	
V_{FRC}/H	$P > 0.05$	$P < 0.01$
V_R/H	$P < 0.01$	$P < 0.01$
V_{TLC}/H	$P > 0.05$	$P < 0.01$
V_{VC}/H	$P > 0.05$	$P > 0.05$
$FEV_{1.0}$/H	$P > 0.05$	$P > 0.05$
C_L/H	$P > 0.05$	$P > 0.05$
R/H	$P < 0.01$	$P > 0.05$
	Group III versus healthy children	
V_{FRC}/H	$P < 0.01$	$P < 0.01$
V_R/H	$P < 0.01$	$P < 0.01$
V_{TLC}/H	$P < 0.01$	$P < 0.01$
V_{VC}/H	$P > 0.05$	$P < 0.01$
$FEV_{1.0}$/H	$P > 0.05$	$P < 0.01$
C_L/H	$P < 0.01$	$P < 0.01$
R/H	$P > 0.05$	$P > 0.05$

C_L = dynamic lung compliance R = pulmonary flow resistance.

TABLE 2 *Relationship expressed in correlation coefficients between the different lung functions and height between dynamic lung compliance (C_L) and lung volumes and between forced expiratory volume during one second ($FEV_{1.0}$) and pulmonary flow resistance (R) and conductance*

	Healthy children		Symptom free asthmatic children: Group I + II		Group III	
log V_{FRC}/log H	(0.962	$P < 0.01$)	0.817	P 0.01	0.407	P 0.05–0.0*
log V_R/log H	(0.937	$P < 0.01$)	0.683	$P < 0.01$	0.118	$P > 0.05$
log V_{TLC}/log H	(0.912	$P < 0.01$)	0.924	$P < 0.01$	0.741	$P < 0.01$
log V_{VC}/log H	(0.897	$P < 0.01$)	0.828	P 0.01	0.701	$P < 0.01$
log $FEV_{1.0}$/log H	(0.884	$P < 0.01$)	0.863	$P < 0.01$	0.606	$P < 0.01$
log C_L/log H	(0.727	$P < 0.01$)	0.677	$P < 0.01$	0.022	P 0.05
log R/log H	(−0.728	$P < 0.01$)	−0.334	P 0.05–0.02	−0.226	$P > 0.05$
C_L/V_{FRC}	(0.784	$P < 0.01$)	0.827	P 0.01	0.400	P 0.05–0.02
C_L/V_R	(0.813	$P < 0.01$)	0.516	P 0.01	0.203	P 0.05
C_L/V_{TLC}	(0.800	$P < 0.01$)	0.600	P 0.01	0.393	$P > 0.05$
C_L/V_{VC}	(0.751	$P < 0.01$)	0.644	P 0.01	0.303	$P > 0.05$
log $FEV_{1.0}$/log R	(−0.826	$P < 0.01$)	−0.464	P 0.01	−0.220	P 0.05
$FEV_{1.0}$/cond.	(0.841	$P < 0.01$)	0.446	P 0.02–0.01	0.385	$P > 0.05$

TABLE 3. *Mean ratios with standard error (ε) and standard deviation (σ). Differences between groups tested by analysis of covariance.*

	V_R/V_{TLC}		V_{FRC}/V_{TLC}		$FEV_{1.0}/V_{VC}$	
	mean ± ε	σ	mean ± ε	σ	mean ± ε	σ
Asthmatic children						
Group I + II	0.235 ± 0.010	0.053	0.424 ± 0.011	0.055	0.781 ± 0.016	0.081
Group III	0.221 ± 0.015	0.064	0.436 ± 0.017	0.072	0.730 ± 0.023	0.094
Healthy children	0.198 ± 0.005	0.031	0.405 ± 0.007	0.047	0.820 ± 0.009	0.053
Diff. {Group I + II / Healthy}	0.037	$P < 0.01$	0.019	$P > 0.05$	0.039	$P = 0.05-0.02$
Diff. {Group III / Healthy}	0.023	$P > 0.05$	0.031	$P = 0.05-0.02$	0.090	$P < 0.01$
Diff. {Group I + II / Group III}	0.014	$P > 0.05$	0.012	$P > 0.05$	0.051	P 0.05

ferent lung functions versus height, for lung compliance versus lung volume and for forced expiratory volume during one second versus pulmonary flow resistance and conductance respectively are listed in Table 5 [31]. As can be seen from the table the correlations are fairly well maintained in *Group I + II*. In *Group III* however only some functions are correlated to height and the compliance/volume

TABLE 4. *Data for the 7 not symptom free children*

	Age	Height cm	V_R l	V_{FRC} l	V_{TLC} l	V_{VC} l	FEV l	Compl. ml/cm H_2O	Resist. cm H_2O/l sec.	VR/V_{TLC} 100	V_{FRC}/V_{TLC} 100	$FEV_{1.0}/V_{VC}$ 100	Breathing rate	Clinical symptoms
	12	160.0	*2.11*	*2.43*	4.05	*1.92*	*0.93*	99	*17.6*	*52.4*	*61.5*	47.2	40	Occasional [illegible] 0 therapy
	14	153.0	*1.76*	*2.86*	*4.55*	2.12	*1.16*	*193*	7.5	*36.1*	*88.6*	*43.4*	40	Occasional prednisolone
K. J.	12	151.0	0.91	1.62	3.93	3.04	*1.65*	119	6.6	23.0	35.5	*45.1*	18	Asthmatic [illegible] day before [illegible] rhonchi at [illegible]
H. S.	10	140.5	*0.99*	*1.75*	*2.61*	[illegible]	*1.42*	99	6.6	[illegible]7.4	48.4	*61.0*	22	Asthmat[illegible] [illegible]
E. Å.	11	142.5	*1.02*	*1.61*	[illegible]24	*1.32*	*0.66*	71	6.3	*43.8*	*70.1*	*50.0*	23	Occasional ephedrine
E. E.	13	152.5	0.77	1.40	[illegible]93	*2.15*	*1.46*	*65*	*10.6*	26.1	47.5	*69.5*	18	Occasional 0 therapy
M. B.	16	16[illegible]5	*1.49*	[illegible]	*4.26*	3.77	*2.09*	*116*	*11.6*	[illegible]8.3	45.4	*57.9*	19	0 [illegible] prior to [illegible]tion

Italicized figures outside the 95 % confidence interval for healthy children.

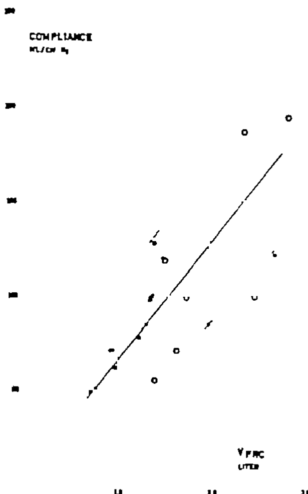


Fig. 6. Lung compliance in relation to functional residual capacity (V_{FRC}). Regression line for healthy children with 95 % confidence interval.

Group I + II symptom-free asthmatic children
Group III

O Not quite symptom-free asthmatic children.

relationship is broken, except for functional residual capacity (Fig 6) where a probably significant correlation exists There is neither any correlation between forced expiratory volume and pulmonary flow resistance and conductance respectively in *Group III* (Fig. 7)

The mean ratios of V_R/V_{TLC}, V_{FRC}/V_{TLC} and $FEV_{1.0}/V_{VC}$ are listed in Table 3 Analysis of covariance of the mean ratios shows that V_R/V_{TLC} is statistically significantly higher than in healthy children in *Group I + II* ($p < 0.01$) but not in *Group III* ($p > 0.05$). V_{FRC}/V_{TLC} is probably significantly higher in *Group III* ($p = 0.05 - 0.02$) but not in *Group I + II* ($p > 0.05$). $FEV_{1.0}/V_{VC}$ is significantly lower in *Group III* ($p < 0.01$) but only probably signifi-

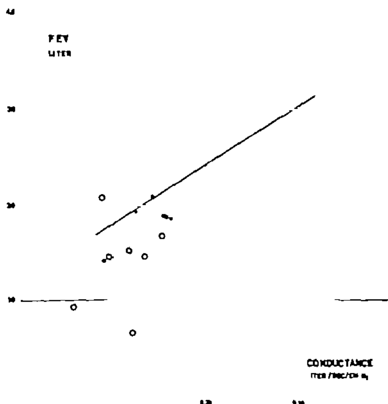


Fig. 7. Forced expiratory volume in one second (FEV) in relation to conductance. Regression line for healthy children with 95 % confidence interval.

Group I + II
Group III symptom-free asthmatic children
○ Not quite symptom-free asthmatic children.

)cantly lower in *Group I+II* (p=0.05–0.0?) Between the two groups there is no statistically significant difference in any of the ratios.

In Fig. 8 the values of V_{FRC}/V_{TLC} are plotted against the values of $FEV_{1.0}/V_{VC}$. It may be seen from the figure that there is a considerable scatter of the values and no trend to correlation when only the symptom free children are regarded.

The data of the 7 not quite symptom free children are listed in Table 4 (see also Figs. 1–9 where they are separately marked). All children have a pathologically decreased forced expiratory volume during one second and a decreased ratio $FEV_{1.0}/V_{VC}$. All children have values of pulmonary flow resistance above the regression line for healthy children with 3 above the 95 confidence interval. Five children have a pathologically increased residual volume and functional residual capacity. However in 4 of these 5 children the total lung capacity is also increased to such an extent that the ratios remain within normal range. Three children of the have a low vital capacity. The values of lung compliance are scattered among the values for the symptom free children with one pathologically decreased and 2 pathologically increased.

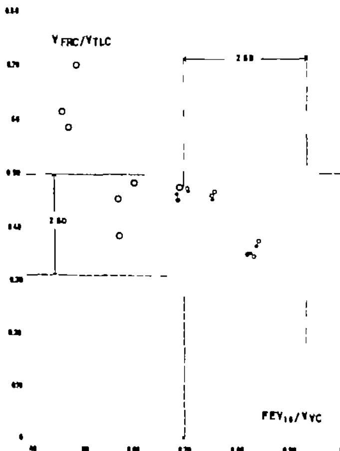


Fig. 8. The ratio of functional residual capacity t total lung capacity (V_{FRC}/V_{TLC}) in relation t the ratio of forced expiratory volume in one second t forced vital capacity ($FEV_{1.0}/V_{VC}$). The 2 SD lines for both ratios in healthy children are drawn.

Group I + II
Group III symptom-free asthmatic children
O *Not* quite symptom-free asthmatic children.

Discussion

In the present study the residual volume and the functional residual capacity are significantly increased in relation to body size in both clinical groups of symptom-free asthmatic children as in hyperinflation. However as the total lung capacity also is increased in the groups the ratios V_R/V_{TLC} and V_{FRC}/V_{TLC} are less increased. V_R/V_{TLC} is significantly higher than in healthy children only in Group I + II and V_{FRC}/V_{TLC} probably significantly higher only in Group III This fairly proportionate increase in residual volume functional residual capacity and total lung capacity found in the groups of symptom free children is more likely due to an overall increase in lung volume than to hyperinflation in the strict sense which should imply an elevation of the end expiratory level i increased ratio V_{FRC}/V_{TLC}. With regard to the individual lung volume

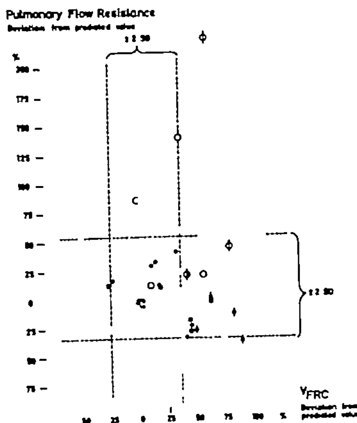


Fig. 9. Percentage deviation of pulmonary flow resistance from value predicted from the relation pulmonary flow resistance/height versus percentage deviation of functional residual capacity (V_{FRC}) from the relation V_{FRC}/height. The 2 SD lines for both functions are drawn.

Group I + II } symptom free asthmatic children
Group III

O As at quite symptom free asthmatic children. Ratio V_{FRC}/V_{TLC} above 2 SD for healthy children indicated by superimposed vertical line.

data the material of symptom free asthmatic children comprises children with mainly increase in residual volume and functional residual capacity and thus high ratios V_R/V_{TLC} and V_{FRC}/V_{TLC}, children with a proportional increase in all lung volumes and children with normal lung volumes. When the material is statistically treated as clinical groups the overall increase in lung volumes dominates.

In a previous study from this laboratory of the static lung volumes in symptom free asthmatic children hyperinflation dominates with significant increases in both ratios in both groups [22]. The hyperinflation found in that study and also in others [3, 25] has been interpreted as mainly functional due to bronchial obstruction. This interpretation has been supported by the effect of bronchodilator drugs [23]. On the other hand an irreversible component with changes in the elasticity has also been discussed. If the functional component of the previously found hyperinflation were dominant it could be assumed that the present material in which the hyperinflation is less pronounced has been studied during periods with less bronchial

obstruction. The same principles for selection and classification have been used in both studies but it is possible that an unintentionally stricter selection of children was performed in the present study. In order to illustrate possible trends at stages closer to asthmatic attacks when bronchial obstruction is more likely to be present also 7 not quite symptomfree children were included in the present study.

A further analysis of the changes in the static lung volumes requires information regarding bronchial obstruction. During asthmatic *attacks* bronchial obstruction has been demonstrated as a decrease in forced expiratory volume during one second ($FEV_{1.0}$) and in the FEVratio ($FEV_{1.0}/V_{VC}$) [11 18 19 21 34] but also directly as an increase in pulmonary flow resistance [13, 32 35]. The $FEV_{1.0}$ in the present material is pathologically decreased (below the lower limit of the 95 % confidence interval) as a sign of bronchial obstruction in all the children not quite symptom free and in 6 symptom free children. The regression line in Group III is statistically significantly lower than in healthy children. The FEVratio is decreased in more children than the FEV giving a decrease in both groups of symptom free children and a pathologically low value in all the not quite symptom-free children. The main explanation for the higher significance in the FEVratio is that the vital capacity is increased in several of the children causing a low ratio even if FEV_1 is within normal limits in relation to body size. Judging from the ratio a considerable proportion of the symptom free children and all the not quite symptom-free children appear to have a bronchial obstruction.

If hyperinflation in symptom free asthmatic children is due to bronchial obstruction a correlation would be expected between a low FEVratio and a high ratio V_{FRC}/V_{TLC}. This, however is not found in the symptom free children but in some of the not quite symptom free children (see Fig 8). One reason for the discrepancy between the ratios may be that $FEV_{1.0}$ can be decreased by narrowing of the air passages promoted by the high intrathoracic pressure during forced expiration [6, 10]. The FEVratio is thus not representative for the condition of the air passages during normal breathing.

For evaluation whether bronchial obstruction forms the basis for hyperinflation and/or for overall increase in lung volume it should be more accurate to correlate pulmonary flow resistance and functional residual capacity as both these determinations are performed during quiet breathing. An analysis of the pulmonary flow resistance versus height shows that only 2 symptom free children and children not quite symptom free have pulmonary flow resistance above the 95 % confidence interval for healthy children. The majority has normal or even low values which gives normal pulmonary flow resistance when the material is statistically treated as groups. This means that in symptom free children there is a very poor correlation between pulmonary flow resistance and FEV and the FEVratio. The correlation between the percentage deviations from the regression lines for functional residual capacity and for pulmonary flow resistance in healthy children are shown diagrammatically in Fig 9. In only one symptom free child and in 2 children not quite symptom free there is

a pathological increase (above the upper limit of the 95 % confidence intervals) in both consistent with a relationship between increase in functional residual capacity and bronchial obstruction. In the other children with increased functional residual capacity there is normal or even decreased pulmonary flow resistance. There is no difference seen between those with a true hyperinflation and those with an overall increase in lung volume. A difference however may be traced between the symptom free and the not quite symptom free children. The latter have all a pulmonary flow resistance above the regression line for healthy children whereas the majority of the symptom free children with high functional residual capacity have a pulmonary flow resistance below the regression line for healthy children.

The differences found in the volume/resistance relationships in the symptom free and the not quite symptom free children allows the assumption that different mechanisms may be responsible for the increase in lung volume during symptoms and during symptom free period. The increase in lung volume during symptoms seems to be consistent with at least a moderate bronchial obstruction in agreement with the generally accepted idea. The increase in lung volume during symptom free period however may be present independently of evidence of bronchial obstruction. The low values of pulmonary flow resistance at hyperinflation found in some children are in accordance with the inverse relationship found between lung volume and pulmonary flow resistance in healthy adults: at higher end expiratory level the resistance is lower [4, 17, 28, 30]. The tendency to low pulmonary flow resistance at high functional residual capacity without change of the end expiratory level corresponds to the inverse relationship between lung volume and pulmonary flow resistance also found during growth [4, 9, 16, 20, 30]. However since the decrease in pulmonary flow resistance is not in all children proportionate to the increase in functional residual capacity it can not be excluded that in some of these children a relative bronchial obstruction may be present as a disproportion between air space and airways.

Lung compliance as a function of elasticity and size of the lungs would be expected to reflect the changes found in lung volumes in this material. During normal growth in childhood the compliance increases in proportion to the increase in lung volume at normal elasticity [9, 16, 20, 26]. Such a proportional increase also is found in the majority of the asthmatic children suggesting an increase in size of the lungs with maintained normal elasticity. In some children however there is a disproportion between lung compliance and lung volume consistent with a disturbed balance between size and elasticity not related to any specific changes in volume or resistance. To draw any conclusions from this imbalance it seems necessary to follow a possible change or persistence in this relationship during periods of changing clinical status.

During an asthmatic attack the lungs and thorax adapt to the disturbed ventilation by increasing the air space. After the attack the lungs and thorax may be assumed to return to a pre-attack status. This return, however, probably occurs at varying rates and is perhaps not always complete. Thus the explanation for the

differences in pulmonary function found in different children and the altered relationships between different functions in the same individual may be that they are studied at varying intervals from the last attack. There is no close relationship between the degree and nature of pulmonary function changes and the clinical classification used. The age of the child, however seems to have some bearing upon the degree and character of pulmonary function change as judged from the slope of the regression lines. This difference may be a coincidence but may also reflect a basic distinction in response of the lungs of the younger and older children.

For further evaluation of whether various responses or various stages in the development mechanisms are responsible for the different changes found it seems necessary to make serial studies on the same children starting with the acute asthma attack.

Summary

1 Dynamic lung compliance pulmonary flow resistance static lung volumes and timed vital capacity were determined in 44 asthmatic children during symptom free period and in 7 children not quite symptom-free

2. The symptom-free children were divided into two groups according to the severity of the disease as judged from the frequency of attacks.

3 Residual volume, functional residual capacity and total lung capacity were significantly increased in both groups of symptom free asthmatic children. Vital capacity and dynamic lung compliance were significantly increased in the group made up of the more severe cases.

4 The ratio V_{RO}/V_{TLC} was probably significantly increased in the group made up of the more severe cases.

5 The ratio FEV $_{1}/V_{VC}$ was probably significantly decreased in the group made up of the milder cases and significantly decreased in the group of more severe cases. FEV was significantly decreased only in the group made up of the more severe cases, and the pulmonary flow resistance was normal in both groups.

6 No obvious relationship was found between signs of hyperinflation and bronchial obstruction in the symptom free asthmatic children.

7 In most of the symptom free asthmatic children the increase in dynamic lung compliance was proportionate to the increase in functional residual capacity

8 The 7 not quite symptom free children all had signs of bronchial obstruction.

9 Th mechanism for hyperinflation during symptom free interval is discussed. Repeated studies in the same individual are required for further analysis.

Acknowledgement

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Department of Pediatrics
Karolinska sjukhuset
Stockholm 60
Sweden

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From the Department of Paediatrics, Children's Hospital,
University of Gothenburg, Gothenburg, Sweden

Reactive Hyperaemia in the Foot and Calf of the Newborn Infant

by OLOV CELANDER and KRISTINA MÅRILD

In previous studies plethysmography has been shown to be a useful method for measuring important functions of the peripheral circulation in the newborn infant. Data on the rate of blood flow in the foot and calf [4], blood pressure determinations [5, 6, 8] and estimations of the capillary filtration coefficient or "CFC" [7] have thus been obtained. By adult standards newborn infants were found to have approximately twice as high a volume flow of blood per unit tissue and also a considerably higher capacity to filter fluid across the capillary membranes. These findings fit well with the concept of a higher metabolism per unit tissue in the newborn.

The generally accepted view [10], that the newborn infant is poorly supplied with blood vessels may be seriously questioned when these observations are taken into consideration. However, the rate of blood flow and also the "CFC" are known to vary within wide limits even during normal physiological conditions, and most tissues are known to possess a considerable local circulatory reserve both as regards volume flow of blood and capillary surface area available for exchange purposes. It will therefore not be possible to draw definite conclusions about the vascularity of a certain tissue until this local circulatory reserve has been explored. In the adult this has generally been achieved by exposing the blood vessels of an extremity to the dilator influences of circulatory arrest, muscular work or a high ambient temperature. Evidently it will not be possible to make newborns work their muscles, whereas arterial occlusion at a high temperature may be tried.

The present investigations were carried out in an attempt to explore the maximal blood flow capacity in the lower limb of the newborn infant. Preliminary data have already been published [4] about some of the observations now described in full.

Method

General principle. A brisk dilator influence on the smooth muscle effector cells in the blood vessels of the lower limb was induced by interruption of the circulation of the limb for ten minutes at 40° C local ambient temperature. The rate of arterial inflow was then followed by venous occlusion plethysmography at short intervals after circulation had been released.

Experimental procedure. The design of the plethysmograph and the general principle in its use on newborn has been described in detail elsewhere [4]. All measurements

were performed in strictly standardized conditions. Thus the hild was put in an Isolette incubator at 30°C. During the period of measurement the child had to remain asleep. After period of adaptation of a least 30 minutes, resting blood flow and arterial blood pressure [6] were measured at a water temperature of 34°C in the plethysmograph. From a reservoir of hot water the temperature in the plethysmograph was then increased to 40°C. An electrothermometer situated at the inlet of the hot water made it possible to ensure that the temperature of the in coming water did not exceed 4..°C. After another period of adaptation of 15 minutes, the rat of resting blood flow and blood pressure were again measured. The sphygmomanometer cuff [5] was then inflated at a pressure of some 20 mm Hg above the systolic blood pressure. As a rule, two separat periods of arterial occlusion were applied. The first lasted five minutes and the second ten minutes. In most cases, the hildren were surprisingly little disturbed even by a ten minute long period of arrest of limb circulation. Many of them became slightly restless or woke up, but, in spite of the fact that the arterial occlusion was maintained, the majority of these children returned to sleep for the rest of the period of circulatory arrest. When this period had come to an end, the pressure in the cuff on the thigh was suddenly released, after which we performed rapid series of flow measurements by short periods of arrest of the venous return by inflation of the cuff at a pressure of 40 mm Hg.

Early in this study we observed that children which had a comparatively low rate of resting blood flow also showed comparatively small increases of flow when a reactive hyperaemia was induced. This phenomenon of a low resting blood flow parallel to a small reactive hyperaemia following circulatory arrest could probably be explained by one of two possible mechanisms. Were the tissues anatomically poor in blood vessels, or was the flow capacity functionally restricted by vasoconstrictor activities of the sympathetic nervous system? To answer this question included in this study measurement on infants which could be expected to be subject to stronger sympathetic constrictor influences than those considered as being in "normal state. The present investigation, therefore comprises three separate series of observations.

React ve hyperaemia at 40°C late neonatal age. This series included 27 infants. They were ll fullterms which upon repeated examination had been considered "normal". Since the adaptation to extrauterine conditions, even t an uncomplicated delivery quit often in ol es marked aberrations from the normal circulatory stat t early neonatal age all hildren in this series were more than 4 hours of age when first subjected to study. Most of them were three t f ve days of age. Many were examined on several occasions. In this case onl the highest peak flow value will be gi en.

Reactive hyperaemia at 34 C irrespective f neonatal age. In this series 31 infants were included. They did not differ from the children in the first series in other respect than by neonatal age. Thus bout half the number of infants in this series were less han 12 hours of age. W expected that these very young children might show a higher constrictor tone by the sympathetic nervous system and that this probably also could effect our reactive hyperaemia responses to circulatory arrest. To add further vascular tone the temperature of the water in the plethysmograph was lowered to 34°C in this series.

Individual changes in react ve hyperaemia during the first week of life. W also noticed that most children, which were subject to repeated observations, showed higher peak flow values at late neonatal age. W therefore included in this study a group of eight infants in which this question was more systematically examined. The first set of observations were performed when the children were less than 12 hours of age (mean age was six hours). At the second examination they were more than 30 hours of age generally three to five days old.

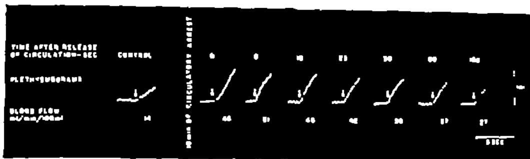


Fig. 1 Reactive hyperaemia in the foot and calf of fullterm newborn infant following 10 minut period of circulatory arrest t 40 C local mbient temperature Original plethysmograms from which the rat of blood flow was calculated.

Results

Observations on resting blood flow and on the hyperaemic response to circulatory arrest have been made at more than two hundred measurements on more than sixty fullterm infants.

Reactive hyperaemia at 40°C in late neonatal age In Fig 1 typical plethysmograms obtained before and after a period of arterial occlusion have been reproduced Since the volume recorder was carefully calibrated at the end of each study and the volume of the tissue enclosed by the plethysmograph wa known, the rate of arterial inflow when a collecting pressure of 40 mm Hg was applied to interrupt the venous return could be calculated from the slopes in these plethysmograms

Fig 2 shows the typical findings when the rate of blood flow was measured after a period of circulatory arrest Thus it wa generally observed that peak flow was higher after a ten minute interruption of the circulation than after a five minute period. Similarly the longer the arrest the more was the hyperaemic response prolonged Two peculiarities in the post ischaemic blood flow curve demand some comments Thus peak flow was never obtained until *five to ten* seconds after the release of circulation.

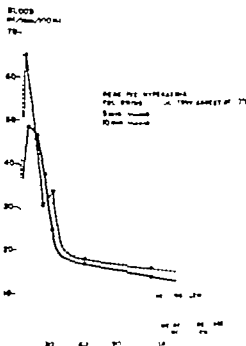


Fig ... Post-ischaemic blood flow curves from which the excess blood fl... during the hyperaemic period was computed. The blood ... fter 5 minutes of arterial occlusion was repe... 60 s during the first tw minutes after circulatory release Not the pe k fl w was higher after 10 minutes of circula ... rrest and that ... hyperaemic period was prol nged A treme... local circulatory reserve ... one

Similar observations have been made on adults by Patterson & Whelan [18]. They showed that this was due to a fall in blood pressure distal to the occluding cuff, and that upon release of the arresting pressure it took 20 seconds or more before the blood pressure regained its previous resting level. Celander & Thorén [8] on medical students measured hand blood flow by plethysmography and, simultaneously made pressure recordings from the corresponding artery These pressure variations upon arrest and release of arterial circulation were then fully confirmed. The shorter interval in newborns until peak flow was reached is probably only a m tter of smaller size of the subjects In Fig 2 the blood flow curve after ten minutes of circulatory arrest shows a "notch" 20 to 30 seconds after the release of circulation. This was quite regularly seen at very big flows. The most likely explanation is that at these very high blood flows through the extremity arterial blood pressure may fall momentarily until adjustments occur over the bulbar cardiovascular centres. This notch should then constitut a so called rebound phenomenon. It seems to be too rapid to be originated by changes in smooth muscle tone in the blood vessels.

Knowing the rate f blood flow during resting conditions, the blood debt created by a period of circulatory arrest could be computed. We could also calculate the excess of blood that was flowing through the extremity during the period of hyperaemia By that we could measure to which extent the blood debt was repaid during the first few minutes. So for example the five-minute period of circulatory arrest shown in Fig was repaid to 60 % during the first two minutes after circulatory release. The ten minute period n the other hand, was compensated for only to some 35 during the corresponding period. Similar observations were made on all infants in this series On dults it has been demonstrated [18] that upon periods of circulatory arrest longer than three minutes the excess of blood flow during the hyperaemic period is provided by prolongation of the hyperaemic flow rather than by any further increase of peak flow values. The latter may then represent the maximal response of the blood vessels to the dilator stimulus of ischaemia Our peak flow values after ten minutes of circulatory arrest are therefore probably close to the maximal flow capacity of the tissues However we did not try longer periods than ten minutes, since any possible damage to the tissues had to be avoided

Fig 3 summarizes our findings as regards peak flow values after ten minutes of circulatory arrest at 40 C in the plethysmograph in a group of 27 normal fullterm infants, studied at late neonatal

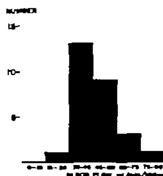


Fig 3. Reactive hyperaemia at 40°C in lat neonatal age. Not that approximately half the number of infants had peak flows from 30 t 44 ml/min/100 ml. A corresponding number had still larger peak flows.

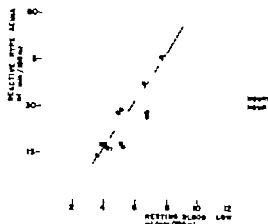


Fig. 4. Reactive hyperaemia peak flows at 34 C plotted against resting blood flows. Note that the very young infants mostly showed restricted peak flow values and also lower resting blood flows.

age. Thirteen of these newborns (almost 50 %) had peak flows from 30 to 45 ml/min/100 ml whereas an equal number had larger flows, and only one child was found to have a lower peak flow value. The mean value for this group was 47 (±1) ml/min/100 ml of tissue.

Reactive hyperaemia at 34°C irrespective of neonatal age. Observations on resting blood flow and peak flow following ten minutes of circulatory arrest are summarized in Fig. 4. From previous studies [4, 7] it is known that resting blood flow normally lies in the region from 5 to 10 ml/min/100 ml. The very young infants (less than 1 hours of age) included in the present series as a rule had smaller flows. The older infants (more than 30 hours of age) on the other hand mostly showed flow values within the previous limits. The most likely explanation for smaller flow values in the very young newborns is a higher sympathetic constrictor tone during the first few hours after birth.

Peak flow values at reactive hyperaemia were considerably smaller in the present group than in the previous group of somewhat older infants, studied at 40 C local temperature. There was also a reasonably fair correlation when the rate of resting blood flow plotted against peak flow values so that children with small resting blood flows also showed restricted peak flow values in their hyperaemic response to circulatory arrest. Since a low resting blood flow most probably is caused by an increase of vasoconstrictor influences on the "resistance" blood vessels these observations suggest that the restriction of peak flow was also due to constrictor nerve activities.

Comparison between early and late neonatal age as regards individual resting blood flow and reactive hyperaemia peak flow. This comparison was carried out on eight fullterm infants. They were examined for the first time before 1 hours of age and then at a second occasion at an age of three to five days. The results in this series are summarized in Fig. 5. As seen, there was a general increase both in restin

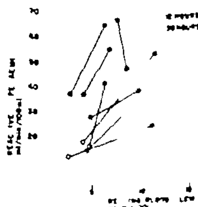


Fig. 5. Resting blood flow and reactive hyperaemia peak flow at 40 C in early and late neonatal age. Note the increase during the first few days after running

blood flow and in peak flow values from early to late neonatal age

There are several possibilities which may explain this change First, the back ground may of course be a rapid development of new small blood vessels during the very first days of life This possibility seems rather unlikely considering the fact that in some subjects the change was established in less than 24 hours Changes in blood viscosity are certainly not concerned, as haemoconcentration rather than haemodilution is to be expected for the first few days. The effect on peripheral circulation would then, if anything be the opposite "Sludging" of blood may be involved. The most likely explanation, however is that the increases of blood flow at late neonatal age both at resting condition and after circulatory arrest, are functional rather than morphological in origin. The observed changes must then be considered as due to release of constrictor tone of the sympathetic nervous system as the adaptation to extrauterine conditions is completed.

Discussion

This communication is the last in a series of papers [4 5, 6 7 8] in which suitable methods to study the circulation of the lower limb of newborn infants have been described, and in which the normal characteristics in these respects at early neonatal age have been reported In the present study we have attempted to explore the local circulatory reserv " in the foot and calf of the newborn by exposing the blood vessels to the dilator effect of ischaemia at a high local temperature We have been able to demonstrate that these tissues showed a striking increase of blood flow in response to th[illegible] man uvre. The peak flow values up t t n times that f resting blood flow were fr quently record ed Thi very high circulatory capacity of the tissues enabled a repayment of the blood debt created by a five-minut period of circulatory arrest to more than 80 % already during the first two minutes after circulat ry release

In adult th reactive hyperaemia following a period of circulatory arrest has been consider d a good indicator of the blood flow capacity of the xtremities both in health and disease F r many reasons however it i rather difficult to compare these responses to circulatory arrest in newborns w th those obtained in similar studies on a ults First the f ot and calf of the newborn i fant have higher percentages of skin and probably l wer of muscle than the adult l mb An estimation of the percentages b v lume d om ponent tissues in the f ot and calf of the newborn infant is [illegible] (progress [11]) Secondly mean arterial bl d pressure (providing the driving forc t blood fl w) is approximately 30 % lower in the new born Blood flow capacity is therefore probably more correctly compared n term of peripheral resistances rather than flow values During resting c ndition "nor mal" fullterm newborn infant have pe ripheral resistances t flow in the lower limb per 100 ml f tissue around 10 PRU (Peripheral Resistance Units) with nor mal variations at standard condition from [illegible] t 14 PRU and with probably definitely pathological resi tances t flow ab ve 20 PRU [6 7]. At reactive hyper aemia after circulat ry arrest per pher l resistance t flow in the f ot fall ext emely and q ite frequently below 1 PRU Th[illegible]

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Department of Paediatrics
Barnsjukhuset
Göteborg
Sweden

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From the Pediatric Clinic (Head: Professor A Lambrechts) University of Liège Belgium

The Influence of the Body Positions and the Orthopedic Thoraco-Abdominal Appliance on the Lung Volumes in Poliomyelitic Patients

by F BONNET F GEUBELLE[1] and C. COFFIN

As the poliomyelitic patients with severe paralytic sequelae cannot continuously be maintained in the supine position [7 14], they will be placed in the sitting and the standing position with the help of a thoraco-abdominal orthopedic appliance and a standing board.

However the clinical observation shows that some patients cannot bear either such or such body position or the orthopedic appliance and complain of respiratory fatigue [2]. These facts have been pointed out previously [4].

The purpose of this study is to measure the changes of the lung volumes when a poliomyelitic patient with respiratory paralytic sequelae is tilted from the sitting to the supine position and is placed in a thoraco-abdominal appliance in both body positions. These results will complete some preliminary observations [8]

Material

The lung volumes have been measured in seven poliomyelitic children (19 determinations) whose biometric and clinical data are given in Table I and Fig 1 Physical therapy undertaken on the limbs and the trunk since the acute phase of the disease was not significantly modified in all the patient but one: in patient no. 5 (Paul) intensive physical therapy to reduce a severe dorsal scoliosis was started between the second and the third assay Physical therapy for the respiratory function has been undertaken since the acute phase in the patients paralysed in 1959 and since the first months of 1959 in the other patients. This treatment includes manual chest-stretching, intermittent positive pressure breathing, active motion of the diaphragm against resistance [5, 16]. The patient nos. 2, 6 and 7 made a daily use of the glosso-pharyngeal breathing (Frog breathing) [2 15]. The orthopedic appliance is usually described as 'thoraco-abdominal appliance' the point of support is on the pelvis, and the thorax and the abdomen are enclosed in the body jacket (Figs. 2 and 3).

Methods

The determinations were taken in the afternoon (2–4 hours after the last meal) successively in the sitting position with orthopedic appliance in the supine position with and without appliance in the sitting position without appliance The determination start when the patient is comfortably settled in the chosen position. The vital capacity (V_{C}) [13], the inspiratory capacity (I_{C}) and the expiratory reserve volume

[1] Associé Fonds National de la Recherche Scientifique

TABLE 1 *Pertinent biometric and chronological data for the 7 poliomyelitic children involved in the study of the lung volumes*

Number and index	Age (year)	Weight (kg)	Height (cm)	Onset of the disease	First determination	Time interval between successive determinations		
1 Camu	.6	18	121	1954	21 10.59	1 month	7 months	—
Mara	5	17.2	110	1954	4 11.59	day	3 months	4 months
3. Lemm	10	4	138	1957	01 1[illegible]9	3 days	3 day	6 month
4 Marm	11.5	35	153	1954	03 02.60	1 day	—	—
5. Paul	16.5	49.5	161	1955	21.09.59	4 days	1 month	—
6. Peri	14.5	47.8	1 0	1955	05.1[illegible]59	1 month	—	—
7 Fran	12.5	33	153	1955	10 03 60	—	—	—

(V_{ER}) are measured with a spirographic system without valves [10]. Duplicate determinations of the functional residual capacity have been taken with a closed system and helium as test-gas [11]. The residual volume (V_R) is the difference between V_{FRC} and V_{ER}.

The so-called Mean error of the method for the determination of V_{FRC} includes the technical error from the apparatus (previously calculated ± 1%) [11] and the variation of V_{FRC} from test to test: the resting expiratory level may change if the reciprocal position of the thoracic wall and of the diaphragm is modified. To calculate this Mean error the individual differences between two successive determinations with 15 minutes interval, in the same body position, have been collected.

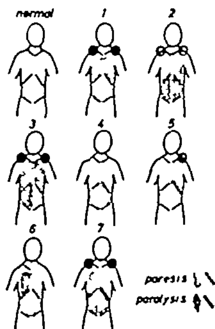
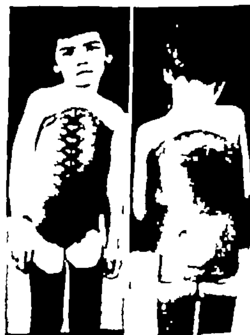


Fig. 1 Sites of paralysis and paresis in seven poliomyelitic children whose lung volumes were measured.



Figs. 2, 3 Thoraco-abdominal orthopedic appliance used in poliomyelitic patients whose lung volumes have been measured.

TABLE 2. *Mean values (M) error (E) and standard deviation* (S.D.) *in 7 poliomyel t c children (19 d terminations) in the sitting and the supine position with and without or thopedic appliance*

	Sitting without appliance			Sitting w th appliance			Supine without appliance			Supine with appliance		
	M	E	S.D	M	E	S.D	M	E	S.D	M	E	S.D
V_{FRC}	971	90	418	784	93	401	722	82	356	6 5	80	349
V_{VC}	1339	140	612	1100	151	850	129	147	633	1196	158	679
V_{IC}	1057	114	498	934	121	525	1217	129	561	10.4	129	56.
V_{ER}	283	35	164	236	35	184	179	24	106	171	28	1 1
V	688	73	316	529	63	273	538	67	290	604	61	287
V_{TLC}	2025	187	857	1697	208	691	1934	203	89	1696	208	892

	Sitting without appliance	S tting with ppliance	Supine without ppliance	Supine with appliance
Mean ± Error	$-27 \pm 16^{*}$	8 ± 23	$+12 \pm 15$	$+19 \pm 13$
Standard deviation	80	99	64	57
Probability	0 166	0.732	0 400	0 160

All the values are expressed in ml and corrected to body temperature ambient barometric pressure and saturated with water vapor (*B.T P.S*)

As none of these differences is significant, the error of the method is calculated (standard deviation of the differences between duplicate determinations divided by the square root of two) and expressed in per cent of the corresponding lung volume:

Sitting without ppliance	56.4 ml i.e. 5 9 % of the mean value f V_{FRC}
S tting with ppliance	70.1 ml i.e. 9.2 % f the mean value f V_{FRC}
Supine without appliance	45.5 ml i.e. 6.3 % of the mean lue f V_{FRC}
Supine with appliance	40,5 ml .e 6 0 % of the mean value of V_{FRC}

This mean error in poliomyelitic children is similar t the one observed in normal children [9] except in the sitting position with orthopedic appliance for which the mean error is larger (9.2 %)

Results

1 The mean values f the individual data are given in Table 2 and Fig 4 The individ ual differences for each lung volume in tw body positions have been calculated (Tables 3 and 4) When the differences are probably significant ($0.05 > P > 0.01$) significant ($0.01 > P > 0.001$) or very significant ($P <$ 0.001) the so-called physiological variation has been calculated as:

$\sigma x / \sqrt{2}$ where $\sigma x = \sqrt{S(x - \bar{x})^2 / (n - 1)}$

2. The results for each patient are presented in Fig 3 the valu for the second mentioned body position is expressed in per cent of the value measured in the first position so that it would reveal the scattering of the successive results in every patient.

* See Appendix.

TABLE 3 *Individual differences betw n lung volume in the sitt ng position without ap pliance minus the corresponding value in the supine position without appliance and the lung volumes in the sitting position with appliance minu the values in th supi pos tion in 7 poliomyelitic children (19 determinations)*

	"Sitting without minus "Supine without appliance						"Sitting with minus "Supine with appliance					
					Physiological variation						Physiological variation	
	M	F	s.D	P	ml		M	F	s.D	P	ml	
V_{FRC}	+240	39	17	<0.001	−1 1	1_5	90	31	125	0.010	93	1.1
V_{VC}	−5_	34	149	0 15	—	—	79	18	80	0.048	—	—
V_{IC}	180	38	167	<0.001	118	11 1	65	31	90	<0.001	43	[illegible]
V_{ER}	+104	18	80	0.001	5"	−"0.1	63	18	1	0.001	29	21
V_{R}	+147	37	163	<0.001	115	−16.8	_3	23	99	0.298	—	—
V_{TLC}	+90	29	1 4	0.006	5	4.2	0.03	_5	110	0.999	—	—

Discussion

A *Influence of body position*

In the sitting position, the poliomyelitic children lung volumes are different from those of healthy children (Figs 6 and 7). One may usually explain the decrease of V_{VC} by the paralysis of the respiratory muscles and partly by the progressive stiffness of the thoracic cage The amount of air in the lung at the end of a normal expiration (V_{FRC}) i at—or below—the lower limit of the normal values (Fig 6 V_{FRC} decreases as soon a the volume of the pulmonary bag or of the thoracic cage (which contains this bag) is reduced

When a normal child i tilted from the sitting to the supine position [9], the decrease of V_{VC}, V_{FRC} and V_{ER} [is usually] explained by the raising of the diaphragm and the abdominal viscera by the change of the lung blood volume [1] and the ela tic properties of the lung [1]. But the part played in these changes by each

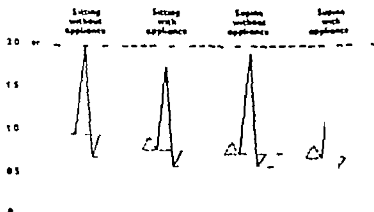


Fig 4 Lung volumes (mean values) in two body positions without and with thoracic appliance For details, see text.

TABLE 4. *Individual differences between lung volumes in the sitting position without appliance minus the correspond ng values in the same position with appliance and ind vidual differences between lung volumes in the supine position without and with appliance in 7 poliomyelitic children (I9 determinations)*

	Sitting without minus Sitting with appliance						Supine without minus Supine with appliance					
					Physiological variation						Physiological variation	
	M	E	s.D	P	ml	%	M	E	.D	P	ml	%
V_{FRC}	+207	34	148	< 0.001	−106	−10.9	+48	23	100	0.062	—	—
V_{VC}	+170	29	125	< 0.001	−90	6.8	+194	36	158	0.001	−112	−8
V_{IC}	122	26	114	< 0 001	−81	.6	+193	34	149	< 0 001	−103	8 7
V_{ER}	47	18	77	0.018	−54	−10	+8	13	55	0.556	—	—
V	+164	28	120	< 0.001	−85	−12.4	+35	23	98	0 180	—	—
V_{TLC}	+325	35	152	< 0.001	−105	5.3	+236	31	133	< 0 001	−94	4 9

above-mentioned factor is unknown. In poliomyelitic children, and especially in those with a bilateral paralysis of the in tercostal muscles (nos. 1 2 3, 6 and 7) the tilting to the supine position has a dif ferent result (Table 5) V_{VC} is unchanged while V_{FRC} decreases more than in healthy children since the abdominal viscera raise the diaphragm and reduce the total volume of the thoracic cage Besides the important decrease of V_{R} in th poliomyeli

TABLE 5 *Differences between l ng volum in sitting and sup ne positions in healthy and poliomyelitic childre*

The significant differences are expressed in of the mean corresponding value in the sitting position.

	Healthy children	Poliom li c children
V_{VC}	−3.3	
V_{IC}	6.	−11 1
V	−14 9	−7 1
V_{FRC}	−9 4	−12
V	0	−14
V_{TLC}	−4	3

tic patients is not explained. the scattering of the values is large (Fig 5) and due to the scattering of the values of V_{ER}.

When the bronchial tree is obstructed in a poliomyelitic patient the supine position is very suitable for a postural draining but reduces the maximum amount of air which could be expired (V_{ER}). While coughing the maximum inspired air (V_{IC}) would be used for a maximum air flow to eliminate the secretions if the expiratory muscles (expressed by (V_{ER}) were strong enough, but both V_{IC} and V_{ER} are reduced in the supine position in poliomyelitic children.

B I fluence f th orthopedic appliance

When the poliomyelitic child is sitting, the thoraco-abdominal appliance brings an important decrease (11 %) of the functional residual capacity (V_{FRC}) It is lik that the thoraco-abdominal appliance would reduce th volume of the thoracic cage by compression of the thorax and or of the abdominal viscera. The r

$$\sigma = \sqrt{\frac{(Sx^2)_p - \frac{[(S x)_p]^2}{n}}{S n - p}} \qquad (2)$$

where

$$(S x^2)_p = (S x^2)_1 + (S x^2)_2 + \ldots (S x^2)$$

$$\frac{[(S x)_p]^2}{n_p} = \frac{[(S x)_1]^2}{n_1} + \frac{[(S x)_2]^2}{n_2} + \ldots \frac{(S x)^2}{n}$$

(p = no. of children)

$$\varepsilon = \sigma / \sqrt{n} \quad \text{where} \quad = S \qquad (3)$$

$$t = \bar{x} / \varepsilon \qquad (4)$$

$$\text{d.f.} = S n_i - p. \qquad (5)$$

When using these formulae the degree of significance does not change in an appreciable way.

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Clinique des Maladies de l'Enfance
Hôpital de Bavière
Liège
Belgium

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From the Department of Paediatrics, County Hospital, Sundsvall and the Department of P thology University of Göteborg, Göteborg

Familial Juvenile Nephronophthisis

by GERT VON SYDOW and STIG RANSTRÖM

The name familial juvenile nephronophthisis (idiopathic parenchymatous contracted kidney) was given, in 1951 by Fanconi, Hanhart von Albertini, Uhlinger Dollvo & Prader [3] to a disease observed by them in two unrelated families. It was characterized by its familial occurrence its insidious onset, usually at bout the age of two to three years with polydipsia polyuria (enuresis) isostenuria, and, frequently retardation of growth, by the absence of hypertension, and by its implacable progression toward death in uraemia after a varying number of years The morphological findings were contracted kidneys with wide-spread atrophy of the tubular apparatus but with focal hyperplasias, with wide-spread hyalinization of the glomeruli and of the basal membrane of the tubuli, with interstitial round-cell infiltrations. However no signs of primary inflammation and no essential vascular changes were evident.

There re comparatively few reports of this syndrome in the literature Hitherto as far as we have been able to find only eight families have been described with the disease [1 3 4 7 ,8] In addition, four single cases have been reported [1] without a positive family history but where the clinical and, in one case the patho-anatomical picture have been so typical that the diagnosis has been considered as established. The reported cases have been collected in Table 1 Until now the disease has only been found in one generation. Consanguinity between the parents of the sick children has been shown in only two cases [3 8] The inheritance has been supposed to be autosomal recessive In two cases [7 4] one of the parents has shown a slightly reduced concentration ability of the kidneys but otherwise no signs of a renal disease possibly this may be regarded as a sign of heterozygoty

Report f the Family E

The *Father* b. 21.9 1901 a road worker; healthy and fit for work.

The *Mother* b. 25 11 1910 healthy; blood and urine have been examined twice with no remarkable findings (see Table 2) Renal dilution test normal.

The father and mother are close relatives in more than one way (see Fig 1). The social and economic conditions f the family were t first unsatisfactory In 1936 the family was described, in a report from the local medical fficer as poor and dirty living four persons in a single room in ow shed The father was then said t be severe lcoholic gambler and wife-tormentor Over the years, the conditions have considerably improved The father has now long been total abstainer and good worker and they live in modern four room house

TABLE 1 *Data on reported cases of juvenil familial nephronophthisis and th ir sibl [illegible]*

Authors		Birth order	Sex	Onset of 1st sign, years	Age at death, years	Autopsy	Siblings
Fanconi *et al* 1951	Fam. St	1	m	2	6	–	
		2	m		6	–	
		3	m	3	6	+	
		4	m		–		
		5	m	–			Polydipsia from 3 years
	Fam. Z	1	m	–			Healthy t 10 years
		2	m	2–3	5	–	
		3	f	4–6	15	+	
		4	f	–			Healthy at 10 years
		5	m	–3	8	–	
Hackzell 10.	Fam. I	1	f	7	8	–	
Enell 1952		2	f	7	9	+	
Hackzell & Lundmark 1958		3	f	–			Healthy at 10 years
		4	f	–			Healthy t 8 years
		5	m	–			Healthy t 1 year
	Fam. II	1	m	6	14	+	
		2	f	7	12	+	
		3	m	–			Healthy at 7 years
Grüttner & Lenz 1957		1	m	4	9	(+)	
Seifert *et al* 1960		2	m	3–6	7	+	
Hooft *et al.*, 1959		1	f	3	9	+	
			m	4	5	(+)	
		3	m	–			Stillborn
		4	m	–			Healthy at 3 years
Broberger *et al* 1960	Fam 1	1	f		9	–	
Ivemark *et al.*, 1960		2	f	–			Healthy at 9 years
	Fam	1	m	–			Died in uraemia t 6 years
			f	8	1	+	
		3	f	–			Healthy t 10 years
	Fam. 3	1	f	10	1	+	
			m	–			Healthy at 10 years
	Fam. 4	1	f	9	–		
			m	—			Healthy t 12 years
	Fam. 5	1	f	1	15	–	
		2	m	5–10			
		3	m	–			Healtly at 1 years
		4	f	–			Healthy t 8 years
		5	m	–			Healthy t 6 years
	Fam. 6	1	m	–			Health t 13 years
			f	2			
v. Sydow & Ranström 1962		1	m	–			Died t 3 month in convulsion
		2	f	4	4	–	
		3	f	10/1 ?			Died at 13 mon h probably in renal disease
		4	f	3	4	–	
		5	m	3	12		
		6	f	6	7	–	
		7	f	–			Healthy at 19 years
		8	f	3–6	9		
		9	f				Healthy at 13 years
		10	m	6	–		
		11	f	–			Healthy t 8 years



Fig. 1 Pedigree of the family E.

1. *Assar* b. 10.12.1930, died at home 10.5.31 (5 months old) in 'convulsions' Not examined by a doctor; no autopsy According to the mother he was always very lax and peevish and probably mentally backward.

2. *Anna-Lisa*, b. 18.10.1932. Rickets in infancy Albuminuria was observed at 11 months but said to be innocent. With the exception of measles, healthy until Christmas 1936 when she had a throat infection with high fever and headache. Thereafter continuously infirm with repeated fever attacks throat infections and loss of weight in spite of good appetite. In April 1937 albuminuria and anaemia were diagnosed and she was prescribed salt and flesh free diet. After severe nose-bleeding, 10.6 1937 she was referred to the medical department, County Hospital, Sundsvall.

On admission thin, very small for her age and very pale. No pathological findings from internal organs; laboratory results indicated severe anaemia and uraemia. Tonsillitis with fever supervened, July 9 after which she deteriorated. July 19 severe dyspnoea, fluttering pulse, fibrillar twitchings. July 21 she was taken home by her parents and died at home the same day (4 years 9 months). No autopsy

3. *Ingrid*, b. 19.4.1935. Looked healthy and developed normally until 10 months of age when she was acutely ill during an influenza epidemic. Thereafter she stopped growing, lost weight and could no longer stand. May 1936, the local doctor made a diagnosis of cystopyelitis and rickets and prescribed a diet which, however the parents could not afford to give her Referred to the medical department, County Hospital Sundsvall, 12.7 1936.

On admission, very small for her age, emaciated dehydrated, pale, silent and pathetic; pronounced rosary and epiphyseal enlargements; marked distension of the abdomen which was filled with hard faecal masses. From July 22, rapid de

TABLE 2. R sult [illegible]

No. Name	Year of birth	Age on examination Yrs	Mos	Daily output	Urine examinations Specific gravity	pH	End creat filtration ml/min.	Albumin (‰)	Sediment leuc	eryth
Mother	10	46	6		1,014				few	
		50	4	333/1 h	1,004 19				few	
2. Anna-L.	32	4	8		1,005 11		..3	0,25–1,5	few	
3. Ingrid	35	1	2		1,01			–	few	
4 Maria	37	3	9		1,002			0 1	abundant	
5. Martin	39	8	3		1,004			–	–	
6. Valborg	40	7	1	17.0	1 002 10			0,1–0..	few	
7 Mona	4	5	4		1,003			trace		
		8	9		1,013				few	few
		10	1		1,014	5.4			few	
		11	6		1,016				few	few
		12	5		1,014				few	
		16	2	1900	1 002 10		124			few
8 Agda M	43	3	10		1,004				–	
		7	3	4100	1 003–06			trace	few	
		7	6	39( )	1 004–03			trace	few	few
		8	6	100	1 006			trace	few	
9 Zaida	45	1	10		1 010				few	
		5	3		1 074				few	
		6	7		1,010	5.4			few	
		8	11		1,005					
		11	9	500/1 h	1 030				2,0 m 12 h	1 5 m 1
10 Bernt-Å.	49	1	11		1 015				–	
		3	3		1,006	5.1			few	
		4			1,011				few	
		5			1,013					
		8	4	40.0	1 004–07		1			
		8	6	1.00/12 h	1 003				–	6 1 m 1
		8	9	1820 + /12 h	1 003				–	6 3 m 1
		8	11	39.0	1 002–06				few	
		9	8	40.0	1 005			trace		
		10	1	2290 +	1 004			0 15	few	
		10	8	9020/1 h	1 002				0 4 m 1 h	6 m 1
		11	4	9000 /12 h	1 001			trace	0 6 m 1 h	0 3 m 1
		1	0	1500 /12 h	1,005				0 2 m 1 h	0 1 m 1
		1	1	35.0	1,004–17	6.1	9	trace	few	
		1	6	18 3 + /12 h	1 004	6.6			9	0 m ..
11 Eva	53	–	7						–	
		1	9							
		4	4	60 + /1 h	1 074				3 m 1 h	
			4		1,007				few	
		8			1 011	6. 5			few	

with frequent w tery tools. Died 43.7.20 (15 month of age) No topsy

4 Maria, b. 1 1937. Said to hav been healthy until aut mn, 1940 when she be came pale and I appearen the local d ctor found albumin ria. Lartus recovered he again f ll III April 1941 w h c .. ra le and lbuminuria. On April 4 he .. re ferred t the surgical department f I Hospit l Sundsvall, f r I hospital [illegible]

Blood examinations

Blood examinations

	RBC mill.	WBC thous.	MSR mm	NPN mg	Creat. mE	Prot. mg	CO_2 mM	N mE	K mE	Cl mE	P mg	Ca mE	Ph-ase K.-A. units
			34	33									
1	4.0	6.4	37		0.8								
4	[illegible]	16.4	59	127									
	6.												
	[illegible]		41										
4	[illegible]	2 .0	70	[illegible]									
			76	96									
1	19	14.7	[illegible]	180		4.2							
			4	29									
			9	34		5.							
1	4.6	5.3	10	34		6.5	78	129		101			
	4.1	6.5	3			6.6	78	119		102	5.4	4.8	13
			4	28		6.4							
1	3.5		11	[illegible]		6.1	[illegible]	134	6.0	93	4.	4.9	7
			4										
1	3.3	9	42	140		6.				89	3.4		
		1 6	22	118		6.0	9						
	9	1 3	45	43		.2	6						
1			3										
			14	39		5.6							
4	4.	4 9	16	31		6.9	22	133		103			
				[illegible]		6.6							
1		0		30			23			100			
				49		3.5					4.3	3.0	14
	3	3.1	1	47		6.4	23	1.3		103			
5	4 5	10 1	1	35		6.0	19	131		104	4.9	3.3	6
			8	39		6.0							
	3.4	4.6	27	63			22			106			
4	3.4	4.2	70	73									
	4.	4.	22	4									
	2.1	4	[illegible]	60		[illegible]	22	14	2.8				
1	4.1	5.3	15	79		[illegible]	15	140	4.		4.4	4.1	11
	4.3	3.5	[illegible]	87		[illegible]				1 9			
	2.3	5	4.	40		[illegible]							
			13	49									
4	2.		39		4.3	.5							
3	2.4	3.5	[illegible]	110	4.1		4	146	5.2	116	7 7	4.3	11
4	[illegible]	6.0	31		4.	6 9	15						
4	4 1	13.	1	[illegible]		5.5							
[illegible]				31		5.6							
6	4.	8 1	13	32		4	19			113			
[illegible]			5			6.5							
5	2.	6.2	6		0 6	6.4	4						

with fever since no surgical disease was found, she was transferred, May 6, to the medical department.

On admission small for her age tachycar- dia, anaemia, very [illegible] an abundance of [illegible] minuria. The [illegible] [illegible]



Fig (Case Martin) Cort with irregula trophy of the t bula ...par tue well as of the glomeruli, interstitial fibrosis and round cell infiltration in trokes perpendicular t the renal surface

of uraemia w th expiratory l spnoea, drowsiness, vomiting: lied the following lay (3 years 11 months) No aut psy

5 *Mart* b *6.3 1930 Measles and mastoidectomy t years. From bo t 3 years on reported to drink t least 2 l ters of liquid per day and t pass large am nt of urine. H urine wa al ay th n and f l smelling nd he had a fo l smell g breath. F m ears f age he wa faint h ering in th

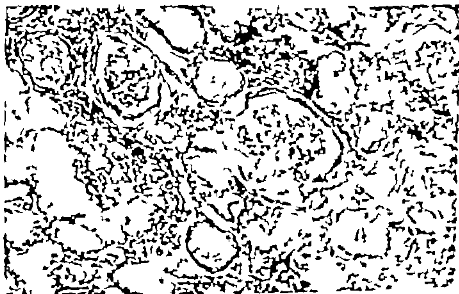


Fig 2. (Case Martin.) Varying degree of fibrosi of Bowman apsule and t ... tion f he glomeruli

mornings and remarkably exhausted following hot baths.

Because of the disease of his sisters taken for examination 29.8.1947. Rather vigorous, ill-nourished boy; remarkably pale with a yellowish tint; slight anaemia and uraemia; very dilut urine; otherwise no pathological findings.

During the subsequent years he went to school every day but required activities were progressively reduced due to his disease. H could not play very much, was usually kept indoors, drank nd urinated a great deal, was unusually fond of salt and always carried some in his pocket.

After having been in bed with influenza for some days he was suddenly seized by repeated con ulsions on the night f 30.12 1950. He as brought to the Department of Paediatrics, Sundsvall, unconscious, yellowish pale, with rattling breathing and died there after a few minutes (11 years months).

The autopsy showed nothing remarkable from the thoracic organs and the digest ve tract. The spleen was small of a light reddish colour. The liver rather small (610 g), light reddish brown without distinct details. The kidney were very small, one kidney weighing just below 50 g, pale with rather wide pelvis and thin cortex, the papillae were well de marcated. The bladder as distended, thick walled, containing an ample amount f pale clear urine.

Microscopic exam nation

Kidneys.—Considerable atrophy f the cortex as well as of the marrow. Especially in the subcapsular parts of the cortex many entirely hyalinized glomeruli re seen, ften assembled in groups and lying lose together due to a considerable atrophy of the t bular pparatus (Fig. 2). Only few glomerul are normally structured and these are often hypertrophic. All transitions can be seen between healthy and entirely hyalinized glomeruli. The fibrosis bviously starts in con nection with Bowman capsule which be comes thickened, compressing the glomerulus. Eventually the latter becomes f brotic after which the entire glomerulus including the capsule will become hyalinized. The capsular space is often dilated before the fibrosis has become solid. Quit normally structured tubuli are not seen, not even in connection wit intact glomeruli. Most tu buli re severely atrophic with hyalinization and thickening f the membrana propria, others are rregularly shaped and slightly dilated, the epithelium is usually markedly atrophic; focally the lumen is filled with a colloidal substance. Interstitially there is an occasionally considerable proli feration f connect ve tissue especially in places where the t bular trophy is most advanced (Fig. 4). Foci f more or less abundant round-cell infiltrations are seen, ften arranged in strokes perpendicular t the renal surface. The tubular hanges ar essentially of the same character in the pyramid and in the cortex. Small stic dilat tions f the tubuli are sparsely noted in the inner regions of the cort x as w ll as in the pyramids. Occasionally slight hypertrophy f the arteriolar walls is observed, but hyalinosis or sclerosis cannot be seen an where. The pelvic mucosa is sparsely infiltrated by round cells. *Lungs.*—Slight hronic congestion, oedema, no inflammation. *Spleen.* Moderat congestion. *Pancreas. Liver. Adrenals.*—Nothing remarkable.

6. I. *Borg*, b. 20.7.1940. Her mother had bserved that her urine like that f several brother and sisters, had always had a strange smell, like cattle dung. Otherwise quite healthy unt l January 1947 when she became pale and faint and had poor appetit. Treated by the local doctor for albuminuria for more than half year t home with bedrest and diet which was strictly adhered t. She had repeated lveolar abscesses during this period. On August 12, 1947 she was taken t the Department f Paediatrics Sundsvall.

On admission small for her age and rather poorly nourished, pale with greenish-grey tint and a slight cyanosis of the lips; small haematomas scattered over th extremities; no oedema. A slight systol murmur over the heart blood pressure 140/90. Severe anaemia and uraemia. Slight albuminuria a



Fig. 4. (Case Martin.) The outer part of the pyramid with pronounced tubular [illegible] trophy and interstitial fibrosis, remaining [illegible] bules are tortuous.

few leucocytes in the casts. Inability of urine concentration and delayed dilution power, the highest dilution being reached [illegible] 10 hours after start of a dilution-concentration test (Fig. 6). During her stay in hospital, she was on the whole in satisfactory condition, interested in the other children, eating well, drinking a lot, sleeping rather much. All the time she emitted a fish-like smell from her mouth. Discharged after some weeks observation. Died at home 5.1.1948 ([illegible] years 5 months). No autopsy.

Mona b. 1.4.194[illegible]. At [illegible] years of age she was prescribed bedrest for a renal infection with albuminuria which, however, has not yet ceased. Measles 19[illegible], tonsillitis with fever several times, otherwise has always been healthy, big and strong; working well as a housemaid. Occasionally admitted to the Children's Hospital for observation, 8.16.6.1950. Tall, well developed girl with healthy appearance; no pathological findings. Laboratory findings always normal on repeated examinations 194[illegible]–195[illegible]. Urine, dilution and concentration test normal.

8. *Agda Märk.* b. 3.10.1943. Pneumonia at 3½ months, treated at home. Always had a delicate [illegible] digestion, alternately hard and loose stool. During 1946 and 1947 repeated [illegible] vomitings. Also [illegible] poor appetite [illegible], drinking much and often; she [illegible] bed-wetting, thin urine, always emitting a fish-like [illegible] chlorine odour from the mouth. Very fond of salt.

Examined 20.9.1947. Very slender and poorly nourished, yellowish pale, no oedema. Severe anaemia, very [illegible]. Otherwise normal findings. [illegible] 1947; [illegible] 1949 [illegible] on the whole healthy until autumn 19[illegible], when she began to be [illegible] the cold [illegible] in loose and [illegible] stay in bed in the month of Christmas 1950, she contracted a cold with fever, cough, earache and dyspnoea. [illegible] slightly confused she was referred to the Department of Paediatrics, [illegible] 1.4.1951.

On admission very small, emaciated [illegible] muscles, yellowish pale, deep rapid breathing, restless, not quite [illegible] red throat [illegible] tachycardia [illegible] murmur. Blood pressure [illegible] demat, anaemia, acid [illegible]. After h[illegible] [illegible] showed considerable improvement [illegible]



Fig. 4. (Case Agda-Märta.) In connection with remaining tubules hyaline thickening of the membrana propria, interstitial round cell infiltration

discharged for further rest at home 11.4. 1951. Two weeks later again admitted after fever and vomitings, but rapidly recovered and could soon be sent home.

Thereafter "healthy" during the summer playing, bathing, taking part in the hay harvest. From November 1951 again pale and tired, had to stay in bed, drank and urinated very much. From March 1952 a certain improvement, could stay out of bed, but complained of difficulty in walking. On April 4, 1952 she again started vomiting; the following day slight convulsions supervened. Referred to the Department of Paediatrics, 5.4.195.., exposed to measles 10 days earlier.

On admission drowsy, dehydrated; moist rales over the lungs; uraemia and acidosis; high fever, semi-comatous, thirsty. On April 8, the first rash of measles appeared. At the same time she had a large haemoptysis and died (8 years 6 months).

The autopsy revealed pale lungs of normal consistency; the main bronchi filled with partly coagulated blood; sanguinolent fluid from the cut surfaces. The myocardium was pale. The liver pale brown, with homogeneous cut surface, weight 490 g. The spleen lax, weighing 40 g. The kidneys small; the ureters were slightly dilated.

Microscopic examination

Kidneys.—Essentially the same histological picture as in Martin's case though the changes are a little less severe: The number of normal glomeruli is a little higher and the tubular apparatus, though the seat of severe changes, slightly better maintained. No cyst formation. Also in this case, no essential vascular changes are seen. *Spleen.*—Moderate congestion, some hyalinosis inside the walls of the penicillar arteries. *Liver.*—Nothing remarkable. *Myocardium.*—Nothing remarkable, except slight hypertrophy. *Thymus.*—Moderately severe parenchymal atrophy.

9. *Zaida*, b. 22.10.1945. Always been healthy and normally developed. Examined several times 1947–1957 always with normal findings.

10. *Bernt Ål*, b. 20.2.1949. Measles 1952 was protracted and followed by diarrhoea, nose-bleeding and transient loss of flesh; whooping cough 1952–53; fever convulsions,

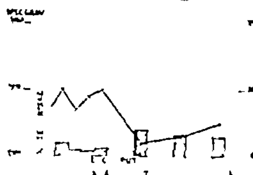


Fig. 6. Urine dilution and concentration tests. V lborg, 18.8.1947 4½ months before death; advanced stage of nephronophthisis.



Fig. 7. Bernt Ak... 7.57. General condition good, diagnosis of nephronophthisis just established.

Sept. 1933; two weeks later found to have obturating tonsils and an increased sedimentation rate; otherwise he on the whole found to be healthy and well developed and presented normal findings on repeated examination 1951 1954. The following year repeated attacks of tonsillitis; on examination at school 1956 found to have a slightly impaired hearing due to otosalpingitis. From the beginning of school autumn 1956 sensitive to the cold in the mornings, drinking heavily, urinating very much and bed wetting every night, but still had a good appetite, was active, energetic and able to ride his bicycle up steep hills without dyspnoea.

Admitted to the Department of Paediatrics, Sundsvall ...6.1957. Slender and rather poorly nourished, pale, good muscular tension, hypertrophic tonsils and adenoid vegetations, slight uraemia, complete lack of urine concentration (Fig. 7). The tonsils were removed under antibiotic protection and he was discharged ... 19... in good general condition.

Since then, he has appeared regularly for check-up at the hospital and has been admitted repeatedly with upper respiratory infection, treated with antibiotics in order to try to prevent further renal damage. He has had periods of increased thirst and fatigue alternating with periods of improvement; on the whole however his general condition as well as the laboratory findings have slowly deteriorated. He does not like sport and actively play any more lessons ... gymnastic and can only participate in the school activities. During his last admission, March 1961 following a urinary dilution and concentration test he went into an uncompensated uraemic and acidotic state which had to be treated by intensive fluid therapy. (At that test the urine appeared more concentrated than usual, and the dilution was delayed (Fig. 7).) Thereafter he recovered remarkably during the summer he was again ... small bicycle and with a good appetite. On his last examination, 1.9.1961 his general condition was rather good, still, he presented a marked anaemia, azotaemia, acidosis and ...

11. Fru ... 19... He has been healthy and developed normally. On repeated examination 1953 1961 ... normal findings.

Comment

It appears from this family report that only three (nos. ... 0 and 11) of the seven brothers and sisters are still alive ... free from signs of renal disease or growth retardation. The fourth ... (no. 10) is suffering from a progressive renal insufficiency. Of the seven deceased children, five have certainly died from a renal disease with uraemia ...

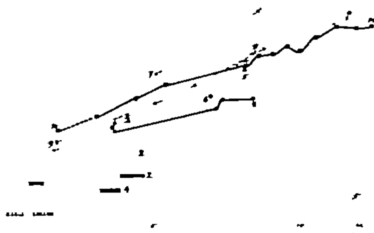


Fig. 8 Body weights (kg) of the children different ages. Horizontal columns: Stippled, possible renal symptoms, open, *renal symptoms with satisfactory general health; filled, uraemic state*

one (no 3) has succumbed to the sam disease. Concerning the first born child. the reports are too defective to permit a determination of the cause of death. All the children with proved renal damage have shown essentially the same development of their disease Insidious start sometime between birth and eight years of age interference with body growth (Fig 8) fatigue pallor sensitivity to cold, loss of flesh and increasing polyuria and *polydipsia The first manifestation and the* aggravations of the disease have usually followed the occurrence of infections. The positive findings on examination have been a poor body development and muscular weakness anaemia and increased sedimentation rat increased values for non protein nitrogen and serum creatinin, renal acidosis (when examined, in untreated cases) almost invariably a low specific gravity of urine and inability of urine con centration; in advanced stages, delayed or ceased ability of urine dilution (Figs 6 and 7) The urine has sometimes contained traces of albumin, the urine sediment has been normal (except one finding of pyuria in a girl) The total serum protein has been normal (as well as the electrophoretic pat tern in one examined case). No increase in blood pressure has been determined.

A patho-anatomical examination was *performed in only two cases The kidneys* in these cases showed essentially the same hanges namely an advanced contraction affecting the glomeruli as well as the tubuli The glomeruli showed varying degrees f fibrotic hyalinization, especially in the subcapsular regions of the cortex, a few glomeruli were entirely normal Concerning the tubular apparatus the tubuli contorti were to a great extent atrophic. The same

was true of the Henle's loops of most nephrons. However, in some nephrons these loops were hyperplastic with dilatation and tortuous convolutions; the epithelium even in these hyperplastic tubuli was to a varying extent atrophic. There was a hyalin-fibrotic thickening of the membrana propria of the tubuli and also a general interstitial fibrosis affecting the cortex as well as the pyramids. The collecting canals of the pyramids were reduced in number. In one case isolated small cystic formations were seen both in the cortex and in the pyramids; in the other case no such cystic formations were seen. In the cortex varying amounts of round-cell infiltrations were found, in some places abundantly.

The clinical course as well as the pathologic anatomy were essentially in accordance with that of previous investigators.

It is difficult from the histologic picture in the autopsy material to arrive at a definite conception of the course of the atrophic process. It has been clear to all earlier investigators as it is to us that it cannot be a question of a primary inflammatory process. Fanconi *et al.* [3] consider the interstitial round-cell infiltrations to be secondary to the atrophy. In those cases where these infiltrations were especially abundant, however, the possibility can hardly be ignored that the non-inflammatory basal disease might have been predisposing to the occurrence of an interstitial nephritis which might have been the cause of the acute deterioration following intercurrent infectious diseases observed in our cases as well as in some cases in the literature. On the other hand some of the acute fever attacks, where the cause was not established, may possibly also be explained not by an infection, but by general dehydration in the same way as has been reported in hereditary renal diabetes insipidus. Concerning the primary renal disease, it seems reasonable to suppose that it initially affects the tubular apparatus. This supposition is essentially based upon the fact that intact glomeruli may be seen surrounded by entirely atrophic tubules, including obviously also the tubular portions connected to the healthy glomeruli. The glomerular fibrosis therefore seems to be secondary to the atrophy of the other parts of the nephron, an opinion which has been maintained by [illegible] *et al.* [ ] and by Seifert *et al.* [10]. The latter authors characterize the disease as a congenital primarily tubular renal insufficiency first involving the distal parts of the tubes. They also regard it as closely related to the congenital renal diabetes insipidus.

The familial occurrence of the disease is possibly still more striking in the present family than in earlier reports due to the great number of brothers and sisters. [illegible] Fanconi *et al.* [3] consider it to be genetically determined. The occurrence of inter-marriages in the pedigree [illegible] support this theory and indicates an autosomal recessive type of heredity. The third ancestral generation consists [illegible] only [illegible] members instead of eight, the fourth [illegible] ten instead of sixteen. [illegible] the occurrence [illegible] arisen by mutation in the ancestry. The fact [illegible] the marriage of a brother [illegible] and a sister [illegible] to nine children, at least four of whom are mentally retarded [illegible] theory. Some facts speak in favour [illegible] assumption that the [illegible] must have happened several centuries ago

The converging pedigree lines go back to a couple born at the end of the 18th century. We know of another family where two children out of nine have died from familial juvenile nephronophthisis, verified by autopsy in both cases. Some ancestors of both families had forbears from the same parish in Northern Ångermanland, but we have not been able to establish a relationship between the two families, though it has been possible to follow most ancestry lines back to the middle or beginning of the 18th century.

Even if it seems that the disease is caused essentially by a genetic factor the possibility cannot be excluded that environmental factors may also have been of importance for its manifestation and, especially for its course. It appears from the case reports that the earlier born children generally fell ill and died at earlier ages than the later-born ones, some of whom seem to have escaped the disease. The disease then, has started earlier and run a faster course at a time when the social economic and hygienic situation of the family was poor than after these factors had considerably improved. This may possibly mean that the later born children have been better protected against infections and dietetic errors and, so, their kidneys protected from provocative strain. Once started however the disease according to our experience will implacably proceed toward lethal uraemia, and all that can be expected from medical care or prevention is possibly some delay of the course.

Summary

Report of a family in which six and possibly seven of eleven brothers and sisters have shown signs and symptoms typical of familial juvenile nephronophthisis, usually from about three years of age. In five of the six established cases death has occurred at different ages between four and twelve years one is still alive at 1 ½ years of age. Autopsy has been performed in two cases, presenting typical findings. Intermarriages between cousins have occurred in the pedigree suggesting an autosomal recessive inheritance. The fact that the onset of the disease as well as the death has generally occurred at an earlier age in the earlier born children than in those born later may suggest that environmental factors have also contributed to the onset and course of the disease.

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(G. S.) Department of Paediatrics
County Hospital
Sundsvall
(S. R.) Department of Pathology
University Hospital
Göteborg
Sweden

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CASE REPORT

Unilateral Renal Artery Stenosis and Fatal Arterial Hypertension in a Newborn Infant

by ARNE LJUNGQVIST and GÖRAN WALLGREN

From the Department of Pediatrics and the Division of Pediatric Pathology at the Department of Pathology Karolinska Sjukhuset Stockholm, Sweden

Arterial hypertension in the pediatric age group is not too unusual a clinical manifestation. It would probably be recognized more often were blood pressure measurements routinely included in the physical examination of a child. As the normal pressure variations in childhood have been thoroughly studied [1 10 12 33] and new more precise methods for pressure determinations in newborn infants have been introduced [2], the detection of hypertension in infants and children is by no means more difficult than in adults.

In contrast to adults, in whom essential hypertension is the most common form [33], this disease is rare in children, only few cases being reported [3 22 30]. In this age group thorough examination can usually delineate a well defined cause for the hypertensive state. These causes may be divided into various groups [26 33] of which the four main ones are: renal, cardiovascular endocrine and neurologic. Renal origin is by far the most common [11] and includes acquired forms of renal disease such as glomerulo- and pyelonephritis, renal tumors [8] renal involvement of lupus erythematodes and periarteritis nodosa as well as congenital malformations of the kidney and/or its vessels. The incidence of hypertension due to cardiovascular abnormalities in childhood is considerable and is related to various aortic valvular lesions coarctation of the aorta and some rare primary angiopathies involving the arterial tree (8, 10 [illegible]). Endocrine diseases which may produce hypertension are adrenal dysfunction [illegible] dromes such as Cushing's disease hyperaldosteronism (6) pheochromocytoma adrenal hyperplasia etc. Finally the neurological causes include expansive and infectious intracranial lesions as well as some more unusual neurological entities like acrodynia and dysautonomia (31).

In early infancy the congenital causes for hypertension quite naturally play an important role. The fact that a number of these cases are amenable to surgical treatment and cure emphasizes the vital importance of early and adequate diagnosis. It is of paramount importance to [illegible] that hypertension due to such a [illegible] defect if untreated may run a [illegible] fatal course. The following report [illegible] tes this in a dramatic way and demonstrates that congenital malformation of renal vessels may produce severe hypertension in the immediate



Fig. 1 The aorta is cut open and reveals the origin of the left renal artery which is stenosed and protrudes funnel-like into the aorta (arrow).

140 mm Hg and ECG showed progressive myocardial damage The patient expired three weeks of age, on the tenth day after admission.

Pathology

Gross examination

Autopsy was performed five hours after the death of the patient. The body was that of poorly nourished and dehydrated male infant and the skin was pale and slightly cyanotic. There were no external malformations.

Abdominal examination showed that the origin of the left renal artery protruded funnel-like int the aorta with stenosis of the orifice to the width of a pin (Fig 1). The renal artery was narrow for the whole of its extrarenal course. The left kidney w slightly smaller than normal, weighing 11 g (normal weight 15 g) and its fetal lobulation was distinct The cut surface showed all medullary pyramids to be discoloured light grey with loss of the normal striation (Fig 2) This hange patchily involved the pyramidal cortex, but as rule the renal columns were



Fig. 2. Frontal section through the left kidney All the medullary pyramids are necrotic (light areas), while the overlying pyramidal cortex is only patchily necrotic and the renal columns as rule are spared. Square indicates the area depicted in Fig 5. Hematoxylin-eosin. 3 ×.

spared. The right kidney wa enlarged, weighing 18 g, but it wa otherwise grossly normal, as wa the renal artery on this side. The renal pelves, ureters and the urinary bladder were all normal in ppearance.

The heart w greatly enlarged weighing 60 g (normal weight 20 g) and the wall of the left ventricle was thickened (LVM 9 mm, RVM 6 mm) No myocardial infarction was seen and the coronary arteries were normal n ppearance nd course Apart from the





Fig. 3 A Fig. 3 B

Fig. 3 A. Microangiogram sl owing the pyramidal cortex and the corticomedullary junc n arteriolae rectae leading t the med lla (right). Left few capsular vessel ... cortical vessel and small glomeruli ... large ... area in the corte ... B. Histologic sect on of the micro ngiographed tissue seen in Fig. 3 A. ... necrotic cortical tissue corresponding t the ... areas ... of Fig. 3 A. Right margin of medullary necrosis ...

tenos t the ori n of the left renal rt ry there were no card ... malformat on.

The con ex surface f the left cerebral hem phere w ... and the c... f ... I ... and ... ten ... and recent hemorr h ... Th had emptied nt the lateral entricl and the blo l had partl ... lated.

The l ngs were dark brown nd hea nd the c... rface l owed area of hemorr hage nd pneumonia. Aerated parench ma was seen ma l long the margins of the lobes.

Microscopic examination

Histology. H t logic xaminat on was performed on both k dneys heart l ngs l er pleen, pancreas adrenal central nervous system and on the gastro ... al tract t ... different level ... tenotic part of the l ft ren l rtery ... small ... The f ... Hemato yl eosin ... for f brinoid ... necr ... tissue ... tained w ... Verh eff ...

The w ll of the arteries ... were normal in ppearance ... the ... and no hanges in their stain ... were ev lent. The part f the w ... renal rt ry that protruded ... was comp sed f a m ... h n ...

The ... areas ... the ... pyram ... were f ... parench ma (F ... 3 B ... the pat hes ... the cort ... med llary j nc ... were ...

crosis involving the major part of the pyra mid with the exception of narrow zone which extended subepthelially along the calyceal recess including the papilla. The necrosis had the haracteristics of pale in farction the cortical aspect of which was bordered by thin layer of loose con nective tissue which contained fibroblasts and capillaries (Fig 4) P tches of necrosis were also seen in the pyramidal cortex but as rule the juxtamedullary zone was spared. Only occasionally were necroses seen in the renal columns, the pelvic ends of which were regularly intact. N vessels were found t contain thrombi. Neither the areas of necrosis nor the intact renal parenchyma displayed sign of inflammatory cell reaction and n primitive structures were evident that would indicate renal dysplasia. There was no evi dence of nephrocalcinosis.

The right kidney was histologically normal and thus without signs of vascular glomer ular or tubular damage. Sections from the left cerebral hemisphere disclosed hemorr hage and necrosis and there were no signs of inflammatory reactions. The lungs were con gested and areas of interstitial and intra alveola hemorrhage were numerous. In ad dition there were extensive areas of broncho-pneumonia with a mainly polymorphonu-clear exudate. Sections of the myocardium revealed no signs of infarction.

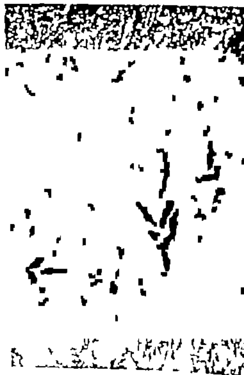


Fig. 4. Section from the cortical aspect of the border of a medullary necrosis. Bottom, necrotic medullary tissue. Center t bular atrophy and interstitial f brosis rich in f broblasts and con taining some irregularly coursing capillaries filled with contrast medium (arrows). van Gieson. 65.

Micro-angiography

Before the kidneys were cut a 7.5% aqueous suspension of barium sulphat (Micropaque) w injected int the renal arteries and the kidneys were placed in 10% neutral formalin at room temperature for 5 days. The kidney were then subjected t stereo-angiographic examination down t the microscopic level according t procedures described earlier [18]. One of the micro-angiographed blocks of the left kidney was sectioned serially for histologic examination, while from the other micro-angiographed blocks of both kidneys, 5 sections were col lected for histologic examination

The micro-angiographic pattern of the right kidney was normal in all respects and no alterations similar t those described in cases of essential hypertension in adult were evident [17] In the micro-angiograms of the left kidney the cortical arteries and arterioles visualized were thinner than those of the right kidney and the glomeruli were slightly smaller In addition, large vascular areas were seen, and these corresponded t the areas of necrosis described above (Figs. 3 A and 6 A). In the medulla these areas were separated from the renal pelvis by narrow zone of arteriolae rectae (Fig. 5 A and 6 A) These originated from arterioles in the juxtamedullary zone at the pelvic ends of the renal columns. Arteriolae rectae were seen t originat all along the corticomedullary junction the normal way but, with

especially in the subcapsular region which is supplied by the most peripheral branches of the cortical arteries. The renal columns on the other hand were as a rule intact and they are supplied by vessel that originate at a more proximal point of the intrarenal arterial tree than the vessel of the pyramidal cortex

The stenosis of the left renal artery found in this case undoubtedly was an example of a true congenital anomaly and had obviously caused severe interference with the circulation of blood through the kidney thu justifying the assumption that the hypertension wa of true Goldblatt type In the absence of further vascular anomalies left ventricular hypertrophy and cerebral hemorrhage con tituted morphologic sign of hypertension Questions arise a to whether hyperten ion had exi ted during fetal life as well and thus ought to be considered a congenital in its appearance If not what factors protected the fetu from intrauterine hypertension? Although th kidneys are known to be functioning early in f tal life [23] their a tivity during gestation i low Thus their metabolic demand is relatively small a placental transfer i responsi le for the main regulation of th milieu intérieur [ ] I st natally however th functional demand upon the kidney i suddenly increased by the full responsibility of maintaining bo ly fluid h meosta i which result in n increase in metal l need and liability to anoxia An impaired renal vasculature that during fetal life wa capable of giving adequate tissue oxygenation mi ht now be insufficient and a lat nt Goldblatt mechani m released

Th clinical and morphologic findings in the present case support th view that a latent Goldblatt mechani m had been present in utero and wa released at birth due to the stenosi of the left renal artery The uneventful latter part of the gestat n together with the normal behavior f th infant in th immediate neonatal peri l thu suggest that the severe hypert nsion had not been present i utero but had developed rapidly postnatally Th presence of renal necrosi indicates that the ischemia wa severe an l ha l dev loped suddenly since a less marked and gradually developing i chemia will not cause necrosi but varying degree of renal atrophy [14] Moreover most f tl necrotic area at the time of death had the character of a few week-old inf rctions which is compatible with their appearance in the immediate neonatal peri l

In experimentally induced hyperten n generalized vascular changes similar t those of human hypertension will often develop The duration and degree f hy perten ion required f r the pr l ct n f these changes differ widely however fr m species to pecies [ ] A to humans nd the newl orn infant in particular n reliable lata are av ilable on thi matter The findings in th present c se suggest that although the hypert n n marked the tim required f r the pr luc tion of vascular chan es had not el psed Thi too support the vi that the hyperten ion w of a fairly recent and that it had probably not been present in utero Th absence of general ze generalized vascular h nges is taken to indicat th t hypertension w reversible [31] nd makes it pr bable th t remo al f the ffected kidney i the present ase would ha been cur

Since the first successful treatment of renal hypertension by removal of the diseased kidney was published [4 16], an ever increasing number of successfully treated cases have been reported. It has been pointed out that the younger the patient, the better the result from nephrectomy [22, 37]. This naturally has emphasized the importance of accurate diagnostic approach in childhood. As the present case illustrates a failure to diagnose in due time a renal origin of hypertension that would probably have been cured by nephrectomy the diagnostic means and their significance deserve special mentioning. Margolin *et al.* [20] reviewed the renal symptomatology in 23 cases of unilateral renal artery obstruction with hypertension. They found that the most common single feature proteinuria, was present in all but two of the reported cases. The i.v. pyelogram was normal in no less than ten out of the twenty-six cases studied, thus proving it to be an unreliable diagnostic tool, as has been pointed out by others [7 34]. Smith & Saylor [36] emphasize that conventional renal function studies are of little diagnostic help as compared with unilateral renal function tests. The most accurate way of detecting unilateral renal vascular anomalies however is aortography or selective renal angiography. This has been frequently emphasized and this investigation should undoubtedly replace the i.v. study whenever a suspicion of unilateral renal vascular disease exists.

The present case illustrates that renal hypertension should be considered in the differential diagnosis of diseases even in early infancy. Although time may be limited treatment may be successful if the diagnosis is made with the least possible delay.

Summary

This is a report of an infant with severe arterial hypertension, who died with cerebral hemorrhage at the age of three weeks. Autopsy revealed a congenital stenosis of the origin of the left renal artery. Comparative micro-angiographic and histologic studies of the kidneys showed the right kidney to be normal, while the stenosis had severely interfered with the blood supply to the left kidney which organ displayed multiple infarctions. Renal ischemia was therefore regarded as the cause of the hypertension and had probably become manifest at birth when the increased demand of blood supply to the kidneys could not be met. The absence of generalized arterial changes secondary to hypertension suggests that removal of the affected kidney would have been beneficial in this case. Renal hypertension should be considered in the differential diagnosis even in early infancy and the importance of early diagnosis of this condition is stressed.

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the family members were thoroughly examined and X rayed for possible signs of the disease. A detailed pedigree demonstrated a double second cousin marriage for the parents.

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(R. L. T.) Genetics Division
Oregon Primate Research Center
Box 366
Beaverton, Oregon
(H. T. L.) 312 Euclid St
Evansville, Indiana
U.S.A.

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CASE REPORT

Dysplasia Epiphysialis Punctata

by ERIK THAMDRUP and B. ZACHAU-CHRISTIANSEN

From the Children Hospital, Fuglebakken, Copenhagen (Head Fell. Tudvad M.D.)

Dysplasia epiphysialis punctata is classi fied in most paediatric manuals as atypical chondrodystrophy placed in the group which generally includes also Ellis–van Creveld s syndrome (chondroectodermal dysplasia), Morquio s disease Hurler s disease (gargoylism) and dysplasia epiphysialis multiplex. Classical chondrodystrophy is also called achondroplasia.

Clinically and radiologically Morquio s disease Hurler s disease and achondroplasia are well-defined and well-known diseases.

Dysplasia epiphysialis multiplex is known primarily from F irbank study [5]. It occurs in children and adolescents, and its signs are dwarfism with short limbs and plump fingers. Some of the patients show bony contractures and few have subluxations. Radiography reveals irregular demarcation of the epi physes, in some cases with fragmentation or slightly mottled configuration. All epiphyses may be involved, most often the hip joints and ankles, less commonly the shoulder and knee joints, and very seldom the spine. The disease undergoes spontaneous regression, but predisposes to osteo-arthritic changes.

The Ellis–van Creveld syndrome, first described in 1940 (Ellis & van Creveld [4]) is characterized by ectodermal dysplasia, especially hanges of the hair nails, and teeth. Other features are p ly dactylia and congenital heart disease The patient are short, the proximal part of their limbs being particularly short. The radiological changes resemble those in achondroplasia.

Dysplasia epiphysialis punctata has been reported under a variety of designations. Originally Fairbank [6] used the adjective puncticularis. Other synonyms are chondrodysplasia foetalis hypoplastica (Conradi [3]) chondrodystrophia calcificans cong (Hunermann [9]) chondrodystrophia foetalis calcarea (Burckhardt [ ]) or just "stippled epiphyses"

The first case was reported by Conradi in 1914 Fairbank in 1949 [6], collected 16 cases from the literature This number was brought up to 35 by Putschar [1.] and to 4. by Mosekilde [11] who added three cases of his own. Since that time Savignac [13], Scott [14], Briggs Emery & Illingsworth [1], and Frank & Denny [7] have published single cases.

The signs have been most clearly described by Mosekilde who emphasized five groups.

(1) Micromelia especially due to short upper arms and thighs.

(2) Special shortening of one or two limbs, a sign which is found in about 50 %.

(3) Joint contractures, generally caused by soft tissue hanges. Tight joint capsules or cutaneous rea s and connective-tissue formation in the muscles

(4) Bilat ral congenital cataract

(5) Characteristic X ray appearances consisting in irregular small calcified spots,

in the *epiphyses* and *apophyses* These changes are most often found in the epiphyses of the large joints seldom in the metacarpals, metatarsals or phalanges They may also involve the spine sternum, and the cartilage preformed parts of the skull most uncommonly the hyoid bone and larynx.

In addition to these main signs a number of patients have exhibited certain more uncharacteristic signs, such as a flat root of the nose a short neck, congenital heart disease malformation of the fingers (adactylia hypodactylia and syndactylia) and cutaneous changes (a dry scaly skin, ichthyosis and exfoliative dermatitis) A few of the patients have been mentally backward.

Maitland [10] has reported the occurrence of the disease in two siblings, but no other familial cases seem to be on record.

Pathological studies have revealed increased vascularization and areas of cellular degeneration and calcification in the articular cartilage [1 8] The patient reported by Briggs *et al* [1] showed signs of heart disease and autopsy disclosed gelatinous excrescences on the mitral valves.

In the literature dysplasia epiphysialis punctata is often mixed up with dysplasia epiphysialis *multiplex* because in both diseases X rays reveal epiphyseal irregularities As already mentioned, the characteristic finding in dysplasia epiphysialis punctata is calcified irregular stippling of the epiphyses ("stippled epiphyses") while in dysplasia epiphysialis *multiplex* the epiphyses show merely varying density ("mottled epiphyses") The calcifications also clearly distinguish dysplasia epiphysialis punctata from the epiphyseal dysgenesis of hypothyroidism

Case Report

A girl, No. 8 of a family of 8. No. 2 had died at the age of one week, allegedly from pneumonia. She was said to have had "fish skin"

The pregnancy had been uneventful, and there was no family history of dwarfism, osseous or articular diseases. Birth weight 3000 g, length 45 cm. No asphyxia. (Royal Maternity Department B Rigshospitalet Copenhagen.)

After birth the baby was found to have strikingly short limbs, polydactylia, articular contractures, and ichthyosiform erythroderma. The skin disease improved considerably within a few days.

At the age of 70 days the infant was admitted to the Fuglebakken Children Hospital. Her appearance (Figs. 1 and 3) was characterized by malformation of the limbs. Considerable shortening of the upper arms and thighs. The left arm was a little shorter than the right On the left hand there was a



Fig. 1 The girl at 8 months of age Note the short neck and hypertelorism.

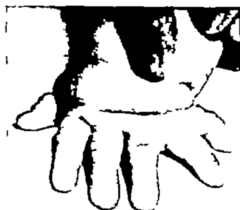


Fig. 2. Same patient as in Fig. 1 The left hand with supernumerary finger

supernumerary ulnar finger and a bud shaped anlage t supernumerary finger on the right hand, fully developed supernumerary toe on each foot The hands and feet were broad and plump. Slight limitation of dorsal flexion in the left wrist flexion of hips only 90° extension f left knee joint only t 1°0° of the right to 150 Corrigible equino-varus position f both feet Paresis f the left radial nerv

The head (Fig. 1) was characterized by a prominent forehead and hypertelorism. Neck short. No goitre Abdomen and external ge nitalia normal. N clinical, radiological or lectrocardiographic signs of heart disease. Skin somewhat red dry and in places scaly



Fig. 3. Same patient as in Fig 1 Supernumerary toe on each foot.

X-ray examination f the skeletal system showed the ppearance haracteristic f dys plasia epiphysialis punctat (Fig 4), with small calcified spots in ll epiphyses in the limbs as well s in the spine and pelvis. Moreover fusion of the left f fth and the supernumerary metacarpal bones.

Ophthalmological examination (t the age of 4 months) A tiny polar cataract in the right eye more pronounced cataract in the left eye with d ffuse densities, especially of the posterior cortex. Ophthalmoscopy revealed blurring on the left but normal ppearan ces on the right The girl could follow light with her eyes.

Histological exam nation of sk biopsy Normal findings in particular n signs of myxoedema (G Asboe-Hansen).

Normal *mbe of chromosome* in the cell nuclei pon blood culture (A Froland)

W sserma reaction negativ *Toxoplasmosis neutralization reaction* Very weakly pos tive 1 10 (50) complement binding not



Fig 4 Hand and foot showing "stippled epiphyses and polydactylia.

performed. *Serum calcium* 5 0 mEq/l *serum phosphate* 4.1 mEq/l, *alkali e phosphatases* 19.3 units/100 ml (King Armstrong) *Protein bound iodine in the serum* 7 0 µg/100 ml. *Serum lipids* Total lipid 768 mg/100 ml, phospholipid 181 mg/100 ml, phospholipid 4% of total, total cholesterol 170 mg/100 ml, free cholesterol 45 mg/100 ml, free cholesterol 25% of t tal, neutral fat 408 mg/100 ml. *Total protein* in serum 6 7 g/100 ml, albumin 4.34 g/100 ml, α -globulin 0.33 g/100 ml, α_2-globulin 0 64 g/100 ml, β globulin 0 74 g/100 ml, γ-globulin 0.66 g/100 ml. Urine: No protein, sugar (Fehling) or phenyl pyruvic acid, negative reaction for mucopolysaccharide. Micr exam. of the urine showed no abnormal constituents.

At the age of 5 weeks the baby could smile, fix her eyes, and hold her head in the prone position. In the course of the first 6 months her mental development appears to have been normal, but —presumably due to the articular contractures—her motor development is somewhat retarded. For instance she is unable to sit without support. The contractures have almost yielded to treatment with splints and physiotherapy The radial paresis has yielded to myotensor therapy The skin is still rather dry and scaly

Discussion

The patient presents all the characteristic main signs of dysplasia epiphysialis punctata set up by Mosekilde In addition, she has a number of other malformations. Hypertelorism a short neck and slight ichthyosis which have been seen also in other cases and polydactylia which does not appear to have been reported previously in cases of dysplasia epiphysialis punctata, while it is one of the main signs of the Ellis–van Creveld syndrome Our patient does not show signs of heart disease or ectodermal dysplasia the characteristic signs of the Ellis-van Creveld syndrome. The mild ichthyosis can hardly be taken to suggest a diagnosis of ectodermal dysplasia The dental development is somewhat retarded but whether other dental abnormalities are present cannot be stated as yet. The hair and nails are normal.

The symptomatology of dysplasia epiphysialis punctata as well as that of the Ellis-van Creveld syndrome is very complex. The fact that the present patient exhibits signs from both syndromes indicates that perhaps the two are not actually separate diseases. In both syndromes the reported malformations affect tissues of ectodermal as well as mesodermal origin which suggest a genetic or exogenou developmental disturbance at the same early stage of foetal life (Uehlinger [15]) In the present case, a chromosome count did not show abnormalities

Summary

Report of the case of a newborn girl who exhibited all the main signs of dysplasia epiphysialis punctata. In addition, she had polydactylia, hypertelorism, a short neck, and ichthyosiform erythroderma.

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The Children's Hospital
Fuglebakken
Copenhagen
Denmark

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PROGRESS IN PAEDIATRICS

Cord Round the Neck

Incidence and Sequelae

by J. SELWYN CRAWFORD[1]

Nuchal cord—the condition in which the umbilical cord is wound at least once around the neck of the foetus—is well recognized as being commonly associated with foetal distress and neonatal depression. It is all the more remarkable, therefore, that little work has been published to demonstrate the incidence of the condition, and to analyse its effects during labour and delivery.

Fitzgerald & McFarlane (6) noted that in a series of 406 cases of foetal distress, there was an associated cord complication in 59 (23 %). In 54 cases there was no other obvious cause of foetal distress, and in 47 (19.7 % of the total) the cord was round the neck. Potts & Ullery (16) observed a nuchal cord, a knot in the cord or a short cord in 57 of 400 cases (14.2 %).

Sciarra (17) draws attention to cord complications being the probable cause of foetal bradycardia (which he defines as a slowing of the foetal heart rate to 100 beats per minute or less for a considerable period) during both the first and the second stage of labour. Wood & Pinkerton (19), on the other hand, say that distress associated with a nuchal cord usually presents itself during the second stage. Hon (8–11), reporting his work with the foetal electrocardiogram, classifies foetal bradycardia (rate 100 per minute or less) into "physiological" and "pathological" types. He claims that the physiological type which is seen during the course of a uterine contraction and is unassociated with disorders of pregnancy or labour is characterized by a sharp drop followed immediately by an abrupt rise to the previous rate—giving a V-shaped curve on the continuously running electrocardiograph. The pathological type gives rise to a U-shaped curve with the fall in rate starting rather earlier in the phase of uterine contraction, and showing evidence of a delay in recovery. Nuchal cord is one of the factors, according to Hon, which may produce a pathological foetal bradycardia, and he designated the effect as being due to cord compression with resultant hypoxia (though he has recently modified this view—see later). Walsh & Lindenberg (18), on the other hand, consider that the nuchal cord may produce foetal distress either by compression of the neck vessels (leading to cerebral oedema and/or hypoxia) or by causing heart failure due to the increasing load on the foetal heart.

Clemetson (3) found comparatively low oxygen saturation in the umbilical arterial blood, but normal umbilical vein blood oxygen saturation in neonates whose cord had been around their neck (whether loosely or tightly was apparently of no significance). Attention has also been drawn by James and his co-workers (1) to the wide umbilical V-A difference in oxygen saturation to be found in this condition.

[1] In tenure of a part time appointment with the Brit. Medical Research Council.

Material and Methods

The present study

Towards the end of 1960 an initial survey wa made of a record system whereby it wa hoped t collect dat regarding the influence upon the neonat of analgesics administered during labour (Crawford, to be published) The study was confined t cases of city booked married primiparae with single preg nancies—involving only patients who had received their antenatal care under the auspi ces of this Unit and who were delivered either in the main Maternity block, or in one of the three outsider M ternity Homes reserved for reasonably normal cases. During the course of the pilot study the high in cidence of nuchal cord, and the prominence of foetal distress and neonatal depression which were possibly referabl t the condition, provoked considerabl ttention. By the time that the main study wa inaugura ted the routine had been adopted of caref lly noting the presence or absence of a nuchal cord t each deli very and of record ing whether or not the cord was clamped and cut prior t complet delivery of the infant T the time of writing 628 cases have been recorded, and they provide the material for this report.

In thi Unit, not made on the pa tient case sheet of the foetal heart rat t intervals of bout one hour during the first half of the first stage of labour (more frequently of course if there is foetal distress) and at half hourly interval during the latter half of the first stage During the second stage the foetal heart rat recorded t intervals of between five and ten minutes. A the patients in this st dy were ll primi parae the majority were under observation from very early in labour

Foet l [illegible] has been presumed on the following evidence: the recording of foetal heart rat (even on a single inst nce) bov 160 beat per minut or below 120 beat per mi t the passage of meconium during labour (except in cases of breech present tion) or post-delivery evidence of it having been passed (g membranes, cord or i f nt meconium-stained, or meconium in the liq or passed immediately after delivery of the infant)

The assessment f the status of the neonat is based upon the Apgar scoring method [1]. In this Unit the Apgar score (Table 1) of every infant is assessed at 1 minute and t 5 min tes after delivery and is noted in detail on the case sheet Not is also made of the time t sustained respiration (T.S R), defined the time, in minutes, elapsing from complet delivery of the infant t the institution of voluntary regular satisfactory respiratory ctivity; times under one minute being noted 'zero Assessment of the T.S R is, of course open to an ppreciable degree f bserver error but it does serve as check on the Apgar score a an infant who has failed to "achieve his T.S R." t the 1 or 5-minut period cannot then have scored 2 point for respiratory effort

The 5-minut score has been i troduced (Crawford [4]) in an ttempt to provide a more dynamic interpretation of neonatal distress than does the simple 60-second score It i held that low score t 5 minutes indicates that the inf nt has been subject t chronic sphyxia (ssociated for example with placent l dysf nction or with prolonged labour), wherea low score t 1 min te and satisfactory score t 5 minutes is more likely to be indicati of a previously healthy infant who ha suffered an acut hypo ia episode lat n labour or d ring delivery

All responsible members of the medical and ursing staff who work i the del very rooms and the theatre have had considerable experience in th is method of ssessing the stat of the neonat and there is reasonable just fication f r accept g the data in th is paper regard g hese ev l ation

Attention has been draw elsewhere (Crawford [4]) the advisabil ty of [illegible] ing the poi t ssigned to [illegible] when defining the presence of neonat l depression [illegible]

TABLE 1 *The evaluation of the newborn infant (the Apgar method of scoring)*
T.S.R. = Time to sustained respiration (in minutes).

	Score		
Sign	0	1	
Heart rate	*Absent*	*Slow* (below 100)	Over 100
Respiratory effort	*Absent*	*Weak cry* hypoventilation	*Good* strong cry
Muscle tone	Limp	Some flexion of extremities	Well flexed
Reflex irritability (*response of skin stimulation to feet*)	*No response*	*Some motion*	*Cry*
Colour	Blue pale	Body pink, *extremities blue*	Completely pink

fants will, because of their thin epidermis and relative lack of subcutaneous tissue, score unmerited points for colour; it is not common for infants delivered by Caesarean section to score any points for colour at one minute though they might be extremely active at that time, and this is possibly a reflection of the lack of the skin stimulation which would *have been sustained had delivery been by* the vaginal rout (Crawford [4])

The A–C (Apgar minus colour) score is, therefore used throughout this paper to afford a definition of neonatal distress. A neonate is defined as having been distressed if its A–C score was less than 7 at 1 minute or less than 8 at 5 minutes, or if its T.S.R. was 1 minute or more

The majority of infants in this series were seen personally for the first time 12–24 hours after delivery and were examined at daily intervals subsequently for as long as their condition warranted

Results

The distribution of methods of delivery was as follows: 454 spontaneous vertex (including 9 anencephalic infants, who will be omitted from further discussion) 114 *forceps* extraction, 46 Caesarean section, 12 breech deliveries

The breech was presented in 6 of the section cases, so that there was a total of 608 *vertex presentations* and of 18 breech *presentations.*

The cases of breech presentation were *too few to allow of detailed analysis. It is,* however of interest to note that in 5 instances (*7 8 %) the cord was around the neck. There was no mortality among the cord group but of the 13 other infants, 3 were stillborn (2 being premature of which 1 was congenitally malformed) and 1 died soon after delivery (renal agenesis)

Of the 608 vertex presentations, 203 (33.3 %) had a nuchal cord. There were 103 vaginal deliveries in the latter group, and *on only 41 occasions (21 %) was the cord* not clamped and cut prior to complete delivery of the infant. Ten of the total 608 cases were delivered by elective Caesarean section (had a nuchal cord), and these will be disregarded in the subsequent discussion, which is thus concerned with 598 cases of vertex presentation, in *01 of which there was a cord round the neck

As will be demonstrated later the incidence of nuchal cord within various ana-

TABLE _. *Incidence of cases of cord round the neck*

Incidence (in consecutive series of primigravidae with vertex presentation, but excluding cases of elective Caesarean section) of cases of cord round the neck—whether cut or not prior to complete delivery of the infant—within each of the groups as defined in the text with the associated rate of perinatal distress. "Late" distress implies evidence of foetal distress manifest only during the second stage or the latter half of the first stage of labour

Group		Nuchal cord	Foetal distress, %		Neonatal depression, %		Late distress (% total distress)	
X 1 (total 135)[a]		91 no cord	31.9		6.6		86.3	
	32.6 %	33 cord cut	45.5	43.2	57.6	23	66.7	81.2
		11 cord not cut	36.4		36.4		78.0	
X 2 (total 113)		73 no cord	22.6		16.7		64.3	
	35.7 %	27 cord cut	37.0	42.5	51.9	28.6	90.0	94.1
		13 cord not cut	53.8		46.2		100	
Y 1 (total 203)		128 no cord	26.3		20.9[b]		71.4	
	32 %	63 cord cut	34.0	38.2	45.2	26.1	81.1	84.0
		12 cord not cut	58.3		33.3		85.7	
Y 2 (total 148)		96 no cord	30.5		24.4[b]		77.1	
	35.1 %	41 cord cut	53.7	53.8	52.	39.3	90.9	89.3
		11 cord not cut	54.5		27.3		83.3	

[a] Excluding 2 anencephalic infants.
[b] Including 2 stillborn infants.

logous categories of spontaneous and operative deliveries was relatively constant. It seems therefore, justifiable to consider the entire series regardless of the method of delivery. It is, however quite unjustifiable to examine the series as a whole when analysing the incidence of foetal distress and of neonatal depression.

It is proposed to group the cases according to a suggestion (Crawford [4]) made in reference to the evaluation of techniques of anaesthesia for Caesarean section. Two main groups are formed (the premature infants should form a third group but as the numbers are small they will be considered within the two main groups in this paper). *Group X* is composed of patients in whom it may reasonably be assumed that placental function is satisfactory. *Group Y* is composed of the other patients, and thus includes cases of pre-eclamptic toxaemia, hypertension, diabetes, prematurity, recent ante-partum haemorrhage, post maturity (i.e. gestation period 4_ weeks and over) and the patients aged 25 or more years (it will be recalled that this series consists entirely of primigravidae).

The duration of labour is also of some significance in the production of neonatal depression, and so the major groups have been sub-divided. *Groups X 1* and *Y 1* are reserved for patients whose labour lasted for less than 1_ hours, and *Groups X-2* and *Y 2* for the remaining patients. (As explained in a subsequent paper (5) further analysis has suggested modification of these groupings, 18 hours of labour rather than 1_ hours being the point of division between Group 1 and _. This modification is not employed in the present article, as it does not influence the

points under discussion) The pertinent details of the groups are set down in Table 2

(a) *Foetal distress*

It will be seen that the incidence of foetal distress is in each group, increased in the presence of a nuchal cord It seems reasonable to assume that a cord which can be slipped over the head prior to complete delivery of the infant has been more loosely applied around the infant's neck during labour than has one which must be clamped and divided. If this assumption is accepted however it can readily be seen that tightness of application of the cord is not an important factor in the production of foetal distress. Indeed only in Group X-1 is a tightly wound cord at delivery associated with a higher incidence of foetal distress than is a loosely looped cord. This finding accords well with the suggestion, made recently by Hon *et al* [11], that the bradycardia and possibly the passage of meconium associated with cord complications results from reflex vagal stimulation The mechanical factor of compression is probably of much less significance than is the foetal haemodynamic change induced by local spasm of the cord vessels

Although, in the presence of a nuchal cord, the incidence of foetal distress varies in an unpredictable manner between the four groups, the difference between general Group X (4 0*) and general Group Y (46.3*) is not great To some extent this *appears to be reflective of* the duration of labour for when the latter is under 12 hours foetal distress is more frequently seen early in labour (the term early in labour connotes the first half of the first stage of labour whilst late in labour defines the second half of the first stage plus the second stage: it is of course a very rough classification) Predominantly however the presence of a nuchal cord appears to induce foetal distress late in labour whatever the duration of the latter

That the presence of foetal distress associated with a nuchal cord did not markedly influence the method of delivery is demonstrated in Table 3

TABLE 3 *Percentage incidence of foetal distress in association with cord round the neck in each group in relationship to the mode of delivery There is no evidence that such distress consistently provoked operative delivery*

Group	Spontaneous	Forceps	C. section
X 1	41 7	57.2	0
X-2	33.6	60.0	16.7
Y 1	40 6	42.7	16.7
Y	33.8	44.0	27.3

(b) *Neonatal depression*

There was no apparent relationship between the observation of foetal distress and the occurrence of neonatal depression in either the cord or the non-cord series. It was more frequently noted in the cord group than in the non-cord group that foetal distress was followed by neonatal depression, but on many occasions this sequence was not followed and in many other cases an infant who was depressed at delivery had given no evidence of distress whilst *in utero*

Only one of the infants delivered with a nuchal cord died (a forceps delivery in Group Y-1) although in the non-cord series there were four stillbirth (one in each of spontaneous and forceps Groups

Y-1 and Y-_) and three neonatal deaths (two in spontaneous Group Y-2, one in forceps Group Y-) On the other hand as indicated in T ble 2 the presence of a nuchal cord almost invariably increased the liability of the occurrence of neonatal depression. It is noteworthy that at this stage of the perinatal history a loosely applied cord—one which was not clamped and cut prior to complete delivery of the infant—is less likely to cause neonatal depression than is one which is wound fairly tightly around the neck

The incidence of depression amongst infants with a nuchal cord—irrespective of the grouping—is notably constant In other words, the role played by the basic obstetric factors of placental function and foetal viability in the production of neonatal depression is obscured when the infants concerned have a nuchal cord The bracketed aggregate figures for neonatal depression in Table 2 brings this point into sharper focus. It seems obvious that this is a fact demanding important consideration when the aetiology of neonatal depression is being investigated and the matter is discussed t greater length in another paper [5]

Attention is drawn elsewhere [5] to the usefulness of the 5-minute Apgar score in helping to differentiate between the de pression due mainly to the acute hypoxic episode of the delivery process, and that sociated with prolonged sphyxia due to placental insufficiency Complete dependence cannot be placed on the 1 minute score to define the gravity of neonatal depression. If recourse cannot be made to biochemical method of assessing the degree of asphyxia then a 5- or 10-minut score seems to provide reasonable clinical

TABLE 4 *Percentage of infants in each group who suffered prolo ged depression i.e. A–C score less than 8 at 5 minutes*

Groups Y 1 and Y 2 of the "no cord" series each include 2 stillborn infants.

Group	N cord	Cord
X 1	0	0
X 2	6.6	2.5
Y 1	7.9	9 2
Y	9 4	3.0

guide In this and other work in process of publ cation [4 5], any infant who scored less than 8 (A–C) at 5 minutes is classified as having suffered severe and prolonged depression. The number of such infant involved in this study is, of course small but as is demonstrated in Table 4 even this response is associated in random manner with a nuchal cord

Furthermore—of the infants who were acutely depressed —that is, those who were depressed at 1 minute but scored 8 (A–C) at 5 minutes a division could be made into two categories—those suffering mild depression (A–C score 5 or 6) and those severely depressed From Table 5 it can be seen that, in cases of vaginal delivery severe acute depression was associated predominantly with nu hal cord

(c) *Other sequela*

It has been demonstrated that in a series of 598 vertex vaginal deliveries of primigravidae (pilot study has confirmed the reasonable sumption that a similar incidence of nuchal cord is t be found in multiparous patient) there w a cord around th neck on 201 (33 4) occasions. Further it ha been shown th t in about 4 cases out of 5 the cord was cut and lamped after only the head of the infant

TABLE 5 *Number of infants in each group who were severely depressed at 1 minute (A–C score less than 5) but who had recovered at 5 minutes (A–C score 8)*

Group	Spontaneous vertex delivery		Forceps delivery		Caesarean section	
	Without cord	With cord	Without cord	With cord	Without cord	With cord
X 1	0	2	0	0	0	0
X 2	1	5	0	0	0	0
Y 1	1	4	0	0	1	1
Y 2	1	1	3	3	3	1

had been delivered. Thus, in more than one quarter (26.8 %) of these vaginal deliv eries the infant fails to receive a transfu sion of placental blood This suggests that the deprivation of a placental transfusion is not of grave—or even moderate—significance to the neonate.

The long term effect of denying infants the 70–100 ml of blood from the placenta is unlikely to be of much significance. It has been shown [15] that, although delayed cord clamping—as compared with clamping immediately after complete delivery of the infant—leads to a significant increase in the haemoglobin levels in the neonates, the distinction between the groups has disappeared by three months after delivery Though it remains to be confirmed it seems reasonable to assume that the infants whose cords were clamped prior to complete delivery are not more likely to be anaemic at three months of age.

It has for long been held that a pla cental transfusion is an extremely im portant factor in the process of adapta tion to extrauterine life made by the neonatal circulatory and respiratory systems. Karlberg [14] has summarized these opinions as follows At the time of birth there is a transfer of up to 100 ml blood from the placenta to the infant and this is accommodated mainly by the pulmonary vascular bed. Physiological studies have indicated that this increased vascular filling may be an important factor in maintaining the stability of the residual volume in the lungs (p 10) And, again "The transfer of blood from placenta to child is certainly of great importance in both respiratory and circulatory adapta tion, and it constitutes one of the impor tant factors in the interaction between these two systems" (p 14) Several wor kers [2 7 13] have implicated the failure to obtain a placental transfusion—or the subsequent loss of the transfusion plus extra siphonage of blood back from the neonate to the placenta—as a factor in the causation of the respiratory distress syndrome

When a nuchal cord is clamped whilst all but the head of the infant remains undelivered there has been little attempt at respiration on the part of the foetus, and indeed, the foetal thorax is being compressed by the walls of the birth canal At this stage of delivery too it is unlikely that an externally provoked pressure gra dient exists between the blood in the pla

cental vessels and the blood in the foetal vessels sufficient to cause a significant re distribution between the two components of the conceptus. In view of the fact that this state of affairs is present in over one-quarter of vertex vaginal deliveries, it is extremely difficult to accept either the suggestion that a placental transfusion is of any importance in the satisfactory adjustment to extra-uterine existence or the postulate that deprivation of this transfusion is a significant factor in the aetiology of the respiratory distress syn drome It must be emphasized that this conclusion does not, of course apply to the cases in which the ("non-cord") neonate, by being held for some time at an appreciable height above the level of the placenta with the cord intact, is actually deprived of a volume of blood in excess of that which it received from the placenta immediately upon delivery

As a commentary upon these conclu sions, one finding of interest may be reported. The majority of the infants form ing this series were seen personally between 12 and 24 hours after delivery and subsequently at daily intervals if the findings were of sufficient interest to warrant it A condition, which has been termed minimal indrawing" was noted in many Patience was required to bserve this. The child had to be lying supine quite still, and breathing quietly On many occasions, under such conditions, a very slight indrawing, occurring during the inspiratory phase of respiration wa observed in the central or lateral sub-costal region The phenomenon wa rarely noted to occur over the intercostal spaces w seen more frequently laterally than in the area round the xiphisternum and was often more marked on the right side than the left.

It must be admitted that this finding is open to considerable scepticism. However the interest lies in the fact that the indrawing is seen more frequently in infants who have had a nuchal cord clam ped than in the rest. It is also seen with marked frequency in infants delivered by Caesarean section, and has not been obser ved following breech delivery

No relationship between the grouping of cases and the appearance of "minimal indrawing" has been observed, but there is a suggestion that infants who have been depressed at delivery are less liable than the others to exhibit the condition There is no relationship between this con dition and the respiratory distress syn drome

In assessing the incidence of the finding observations on premature infants had to be discarded as the weakness of the thoracic cage of these infants tends to give a bogus picture of minimal indrawing A total of 444 mature infants delivered vaginally (vertex presentation) comprises the series. The incidence of indrawing wa s follows: no cord (total 337) 25.5% cord cut (total 107) 42.1% cord not cut (total 3*) 31 2%.

Of the 30 mature infants delivered by Caesarean section 18 exhibited this condi tion

It might w ll be that this response is the only clinical representation f failure to achieve complet lung expansion result of deprivation of placental transfu sion To determine the validity of the bservation more sophist cated method of xam nation of the neonat would be required

The duration of indrawing could not be correlated with any other factor In the great majority of cases it disappeared during the period from 48 to 96 hours after delivery but occasionally it was observed to persist for as long as 7 or 8 days. 'Minimal indrawing' was not looked for until the infant was at least 12 hours old, as it was felt that other factors might confuse the issue during the early neonatal period.

Conclusions and Summary

This report is concerned with 628 consecutive deliveries, the mothers being married primiparae with single pregnancies, living in the city of Aberdeen, and whose ante-natal supervision and delivery had been conducted by the staff of the Obstetric Unit The two anencephalic infants have been excluded from further discussion.

In one-third of the 608 cases of vertex presentation the umbilical cord was found to be around the infant s neck at delivery

The cord was found to be round the neck in 5 of the 18 cases of breech delivery

The 598 cases of vertex vaginal delivery were analysed further a subdivision of the whole being made on the basis of assumed placental efficiency and of length of labour It was shown that nuchal cord whether loosely or tightly applied at delivery was associated with a considerable rise in the incidence of foetal distress, (identified by the finding even on a single occasion, of a foetal heart rate outside of the limits of 120–160 beats per minute or by the passage of meconium prior to delivery) in each group The distress referable to a nuchal cord occurred predominantly in the late stages of labour

A nuchal cord was associated with an increased incidence of neonatal depression in each group the diagnosis of depression being based on the evaluation of the Apgar scoring, colour being disregarded. The increase was greatest in the series of infants whose cords were cut and clamped prior to complete delivery The raised incidence appeared to be haphazard bearing no relationship to the groups and the importance of this finding is to be discussed in another publication (Crawford [5])

Note has been made that the occurrence of a nuchal cord appears to be as frequent in multiparae as in primiparae

Attention has been drawn to the fact that, in 26.8 % of vertex presentations delivered vaginally the cord is clamped and cut when only the head of the infant has been delivered, and that thus an appreciable proportion of infants are deprived of a placental transfusion. The implications of this observation have been discussed. A condition of 'minimal indrawing' in mature infants—unrelated to the respiratory distress syndrome—has been described, and its notable association with 'cut cord' and Caesarean section and its apparent absence following breech delivery has been remarked

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621 Stonegat Road
Moortown
Leed 17
England

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SUMMARY OF SUPPLEMENTS

Overweight Children

by MATS BÖRJESON

(*Supplement 132*)

The literature on obesity and overweight in children shows a lack of reliable frequency calculations. Neither physiologic variations in subcutaneous fat during childhood nor the role of genetic factors have received sufficient attention in the discussion on the etiology. Previous workers in this field, moreover have arrived at divergent results not only in their investigations of the family situation but also in regard to the causal significance of somatic and psychic factors in obesity and overweight. Furthermore, there are no objective investigations into the physical potential of these children and into their relations with other children. The few prognostic studies reported have been mainly concerned with highly obese children and thus shed no light on the question whether overweight of lower grades calls for preventive measures.

The investigation here reported was designed to illuminate these problems by analyses of series collected from all the schools in Stockholm.

By overweight is meant in this study a body weight exceeding the mean plus twice the standard deviation (sigma) at a given height according to current height-weight tables.

The overweight series consists of 718 girls and 687 boys between the ages of 7 and 15 years, and reported as over weight by the relevant school nurses. This series is compared in various respects with two different control series one of them (control series I) comprising 415 girls and 387 boys; the other (control series II) 164 overweight boys referable to one age category (1943) The two control series are also used for checking the reliability of the school nurses reporting as well as the current applicability of the above-mentioned height-weight tables. (Chapter °)

It is clear from the findings that the frequency of overweight children is dependent on both sex and age The girls exhibited frequency peaks at an average age of 9 6 and 14.5 and the boys at age 11 7 and 14.5 years. The series was divided into two groups on the basis of the age at onset of overweight these t o groups being named the O and the P series. The O cases in contrast to the P cases, had already been overweight at age 7 The variation with age was found to depend largely upon the variable frequency of P cases. An analysis indicated that the overweight of these cases was due to physiologic fat parts

The weight distribution of the O cases

suggested that they constituted plus-variants in a continuous variation. The observed frequency of ≥ +2 sigma however somewhat exceeded that expected (estimated from the tables), moreover the series exhibited a shift towards higher overweight grades on comparison with the expected values. Earlier theories regarding the etiology and treatment of overweight are discussed on the basis of the present results. (Chapter 4)

In order to study the significance of genetic factors in overweight the siblings of some of the O children were investigated. These siblings exhibited a weight distribution consistent with that of control series I, though shifted approximately one sigma in the positive direction. When the O cases were divided into a heavier and a lighter subgroup, the respective siblings differed only very slightly in weight distribution. One group of 22 dizygotic twins showed no greater similarity in body weight than did other siblings.

The weight distribution of the siblings affords no indication that overweight may be caused by disease or injuries, or even by major genes. On the contrary the findings suggest that O children actually constitute positive extremes in a continuous variation which is largely due to multifactorial inheritance. The role of possible environmental factors is discussed. (Chapter 5.)

The assumed significance of heredity is supported by the observation that O cases had a higher mean birth weight than controls even though no difference in the average length at birth was recorded. (Chapter 6)

As regards the family situation of the overweight children, the frequency of O and P cases was found, on comparison with controls, to be higher in social group III than the expected frequency. This departure from expectation is assumed to be dependent more upon genetic than environmental factors. The frequency of divorced parents was equal in the two series, whereas parental mortality was somewhat higher in the P group and in O groups of high overweight grades.

In the families of O cases the average number of children declined with rising overweight of the relevant children, and coincidently there was a rising frequency of only-children. This finding might be accounted for by assuming that the fertility of overweight parents is impaired, in which case the only-child situation *per se* would have no etiologic bearing on the child's overweight. An investigation of the 174 only-children in control series I, whose weight distribution was virtually identical to that of the total control series, supports this hypothesis. (Chapter 7)

Analysis of the general morbidity in the overweight series and the controls provided no evidence that maternal disease during pregnancy obstetric complications, or diseases of the child itself had any causal relationship to the overweight. Nor was overweight associated with an elevated incidence of somatic disease or psychic disorders. (Chapter 8)

Th physical working capacity of overweight children in relation to heart volume total hemoglobin and body weight was studied in a selected group of boys. On comparison with controls these O boys were found to have a reduced working capacity. The corollaries with

regard to etiology and therapy are discussed. (Chapter 9)

Since both overweight *per se* and the demonstrably impaired working capacity could affect a child's popularity with its playmates, a number of boys of varying overweight grade were subjected to a sociometric study along with controls. In this study the classmates' choice of companions for three envisioned activities (cinema-going, cross-country running and school work) was recorded. The rating of slightly overweight boys was in no respect poorer than that of the controls. For the envisioned activity of cross-country running the highly overweight boys, on the other hand, had much lower scores than the controls. This result suggests that an impaired physical working capacity is of greater significance than overweight *per se* as a cause of unpopularity. (Chapter 10)

With the aim of studying the prognosis 157 boys of varying overweight type were followed up at an average age of 16 years. Of the P cases, 52 % showed weight normalization. The corresponding figures for the lighter and the heavier O subgroups were 32 and 22 % respectively. Relatively the prognosis was best for the heavier O subgroup probably because it had been subject to control and treatment from the very outset.

Estimation of the risk of 7-year-old boys at +1 to +2 sigma weight level being overweight at age 16 yielded a minimum figure of 3.5 %. The corresponding figure for year-old boys at 0 to +1 sigma level was 0.1 %.

The results are considered to indicate that preventive control or treatment is advisable from the very outset of schooling for all children at weight levels exceeding +1 sigma. (Chapter 11)

Rubella During Pregnancy

A Follow-Up Study of Children Born after an Epidemic of Rubella in Sweden 1951 with Additional Investigations on Prophylaxis and Treatment of Maternal Rubella

by ROLF LUNDSTRÖM

(Supplement 133)

When it appeared in 1951 that an epidemic of rubella was prevalent in Sweden, an inquiry was made at all relevant hospitals for the purpose of collecting a series of maternal rubella cases and of women exposed to rubella in pregnancy without overt disease as the basis for a statistical analysis of the mortality and the frequency of congenital anomalies in the offspring. A control

series was selected from parturients whose case numbers immediately preceded those of selected rubella cases. The inquiry which lasted from July 1 1951 through June 30 195* concerned about 100 000 pregnancies and aimed at investigation of all pregnancies complicated by rubella during the epidemic. Comprised in the analysis were 1159 children of 1146 mothers with histories of rubella. First trimester rubella cases totalled 463 The children of 1340 women exposed to rubella in pregnancy without overt disease and of 713 women selected for control purposes were—as well as the rubella children—subject to a follow up study at 1–3 years of age

The frequency of *spontaneous abortions* was found to be higher in rubella cases than in the controls and in the general population (54 post rubella abortions were available for study) The frequency of abortions after maternal rubella could not be reliably calculated.

Since total recording of rubella-complicated pregnancies was obviously out of the question, the percentage of non-included cases was estimated The possible biasing of the results by such cases was discussed and was found to be nominal

Stillbirth and mortality rates were significantly higher in the first trimester rubella group than in the control group

The first trimester rubella group showed a significantly higher incidence of congenital defects and subnormalities than th controls.

Deaf ss and *chorioretinitis* were found only in rubella children, who also showed a higher incidence of *congenital heart defects* and of *congenital cataract*

Immaturity subnormal length and weight at birth subnormal height and *weight at follow up subnormal circumference of the head* and *retarded functional development at follow-up* (as shown by inability to sit and/or stand before the ages of 10 and 16 months, respectively) were found in higher incidences in the first trimester rubella children than in the controls.

Significant differences were found in respect to the following defects by comparing the incidences for the first trimester rubella group with those for the controls:

Meningocele, dacryostenosis, cryptorchism nd *delayed eruption of deciduous teeth.*

Significant correlations were found between rubella syndrome defects and *intestinal atresia syndactylism hypospadias hydrocele* and *neonat l purpura.*

These findings gave rise to suspicion of an association between maternal rubella and the relevant defects. This was discussed and compared with earlier reports.

Comparison of first trimester rubella children manifesting rubella syndrome defects with those not exhibiting such defects, revealed significant differences in the following:

Length and *weight at birth* and *follow up circumference of the head* and *retarded functional development.*

Comparison of first trimester rubella children not exhibiting rubella syndrome defects with the controls disclosed the same significant differences—with the exception of delayed functional development. Several children who did not exhibit syndrome defects t follow-up were subsequently found to have hearing defects.

A comparison of the *immature* (birth weight ≤ 2500 g) *first trimester rubella*

children with the immatures of the control group showed that the former were born after significantly longer periods of gestation had a higher rate (not significant) of survival and were in general larger than the immatures of the control group At follow up in contrast, the rubella children showed a higher—though not significantly higher—frequency of subnormal height, weight and circumference of the head than did the immature controls. The rate of congenital heart disease was the same (10 %) in the two groups, while congenital cataract chorioretinitis, and deafness were found only in the first trimester rubella group.

That the frequency of congenital cataract, deafness, and congenital heart disease following first trimester rubella in pregnancy is higher than in control cases is well documented The incidence of rubella syndrome children varies in the different studies, however and in the present study it is relatively low i.e. a risk of 10 %. This figure is subject to bias by the following lack of medical diagnosis in the majority of cases and possible inaccuracy of maternal recall of date of attack. The extent of bias and the limits of risk were estimated by a special calculation which gave a *confidence interval for the risk of 7 to 17* % The corresponding interval for 469 first trimester rubella cases collected from the literature (Table 20) was 16 to 23 %, significantly higher than that of the present series. It shoud be noted here however that the two largest previous series (Manson *et al* 1960- Siegel & Greenberg 1960) showed incidences similar to those of the present series. The other previous series were small.

Maternal rubella within the first fifteen days after onset of last menstrual period was observed in 47 women Only one of the offspring exhibited rubella syndrome defects (2 %).

In a preliminary study the present author found that the offspring of *immune pregnant women exposed to rubella in the first four months of pregnancy without overt disease* showed a higher incidence of anomalies than did the offspring of the controls. This finding however was not substantiated at follow up some of the IE children who had exhibited neonatal abnormalities being found normal at the later examination.

As between the *children of non immune women exposed* to but not manifesting rubella and the control children no differences emerged.

The present study is being continued. Investigations concerning the mental development of children whose mothers contracted rubella in the first five months of pregnancy as compared with a control series, are now in progress. A pathoanatomical study of foetuses from legal abortions after maternal rubella is being made with the aim of establishing more precisely the correlation between the stage of embryonic development and the degree of foetal damage.

At present deliberate exposure of girls to rubella seems to be the only practical means of *active immunization* against maternal rubella.

Passive immunization is a possible means of protection for women in the first four months of pregnancy after exposure to rubella. Convalescent gamma globulin 12 %, 4 ml seemed to have had an appreciable protective effect in 51 exposed women—an attack rate of 4 and a total

incidence of 1.2% for rubella syndrome defects in the children following treatment being considered a satisfactory outcome An increase of th dose to 12 ml was proposed, however with a view to possible improvement of the results. Since controls could not be obtained for the series, no far-reaching conclusions could be drawn from the results. A method of selecting controls for future trials was suggested.

Treatment with convalescent gamma globulin in 28 pregnant women with manifest rubella in pregnancy proved inefficacious for the prevention of rubella syndrome defects in children following maternal rubella in the first trimester

The risk of congenital defects following *maternal rubella as an indication for legal abortion* remains a controversial issue Accumulating knowledge of the risk has however led to a growing tendency towards conservative management of rubella complicated pregnancies. On the basis of recent prospective series of extensive size including that studied here the overall incidence of incapacitating rubella syndrome defects has been estimated at 10 %. The opinion of the present author is that —ethical considerations aside—abortions should be induced after maternal rubella only when other factors constitute an indication for interruption of the pregnancy

Desirable measures for combatting rubella in the future would be

(1) Legislation to make rubella a notifiable disease and

(2) Isolation and propagation of the infective agent in the laboratory making possible the elaboration of reliable diagnostic methods and the development of a vaccine

Shunt Operations in Morbus Caeruleus

Results in 161 Cases and Clinical Follow Up

by TAGE MÖLLER

(*Supplement 131*)

The operation in which an artificial communication is created between the aorta and the pulmonary artery was introduced by Blalock & Taussig in 1944 and may be regarded as a milestone in cardiac surgery The operation was designed as a palliative measure to increase the flow of blood to the lungs, which is diminished in the tetralogy of Fallot, tricuspid atresia and haemodynamically similar congenital malformations, and thereby to improve the arterial oxygen saturation in the systemic circulation.

The aim of the author's investigation was to assess the results of shunt operations in cases of morbus caeruleus The

postoperative condition of the surviving patients was investigated with respect to physical development, exercise tolerance cardiovascular status and function of the anastomosis.

The series consisted of 161 cases of morbus caeruleus in all of which the pulmonary circulation was reduced. After special investigations, shunt operations were performed at Kronprinsessan Lovisa s Children s Hospital or at Sabbatsberg Hospital during the period 1947 to 1957 In 148 cases the Blalock–Taussig operation was performed and in 13 cases direct anastomosis was made between the aorta and the pulmonary artery according to Potts. When possible, the follow up investigations included heart catheterization and angiocardiography in order to determine if the shunt operations were followed by secondary hypertension in the pulmonary artery When progressive cardiac enlargement occurred after the operation the author tried to elucidate the cause Shunts created during early infancy were studied with respect to functional efficiency later in life when demands on th circulation had increased.

The postoperative investigations were made by the author in 100 cases at Kronprinsessan Lovisa s Children s Hospital. Ten patients were examined at other hospitals in Sweden and six were examined at Finnish or Norwegian hospitals. Of the remaining 19 survivors, most of them foreign subjects all but two presented written reports concerning their state of health Ninety-seven patients were hospitalized for the follow up investigations and of these patients 89 were studied by heart catheterization and 63 by selective angiocardiography

The follow up studies were concluded at the end of 1958 The observation period from the date of operation ranged from 4 months to 10 years 10 months. The mean observation period was 5 4/1° years and the median 5 years 10 months

Twenty two patients (13 7 % of the series) died in association with the Blalock–Taussig operation. The surgical mortality was higher in children younger than 5 years as compared with older children There was no sex preponderance in surgical mortality The influence of variations in the surgical procedure is discussed. The causes of death are analyzed and also the transient surgical complications and their symptomatology

There were nine late deaths during the follow up period. These cases are discussed with respect to the nature of their congenital malformations cause of death and duration of survival.

Slightly more than 12 % of the children were prematurely born. This is approximately double the incidence of prematurity in a general Swedish population.

The maternal age and the order among siblings did not seem to be significant for the congenital cardiac anomalies. Nor was there any striking familial incidence of such anomalies.

One of the most prominent symptoms of morbus caeruleus is cyanosis. Four grades of cyanosis were recognized. In 64 % of the children cyanosis was manifest before the age of 7 months. As a rule it was the first sign of cardiac disorder and appeared before the diagnosis wa medically established. After shunt operation the severity and incidence of cyanosis were greatly diminished. The best results as regards cyanosis were obtained in children

who were older than 8 years at operation The physical capacity as reported by patients and relatives, and the walking capacity as judged by the author showed considerable improvement after shunt operations when age was taken into consideration.

Systolic murmur was heard before operation in 157 of the 161 cases. In one of the other cases there was only a diastolic murmur in one a continuous murmur and in two cases no murmur was heard before operation. Phonocardiographic follow up showed the preoperative murmur to be unchanged in 96 % of the examined cases In the remaining 4 % the position of the murmur had shifted from the middle to the first half of systole In 86 % there was an additional continuous murmur which was interpreted as a sign of functioning anastomosis.

After anastomosis between the subclavian artery and the pulmonary artery the blood pressure in many cases became measurable also on the side of the operation. This was considered to be a result of the collateral circulation. The pressure in the pulmonary artery could be measured in 41 cases before operation and in 44 cases after operation. In 16 cases readings were available both before and after operation. The preoperative pressure in the pulmonary artery was invariably normal or subnormal. In th cases in which comparisons could be made there was a statistically significant rise in systolic and diastolic pressure after operation. The pulse pressure in the pulmonary artery was also increased after operation but the rise was not statistically significant Pulmonary hypertension is probably not of primary importance for the prognosis after shunt operation for morbus caeruleus. The oxygen saturation in the systemic circulation increased significantly after operation and the haemoglobin, correlated to th oxygen saturation showed a tendency to fall towards normal values.

Comparisons were made of preoperative and postoperative electrocardiograms. In statistical analysis of the atrial complex, no significant change in amplitude was found after operation over the right side of the heart but there was significant diminution over the left side The ventricular complex likewise was unaltered over the right side of the heart, but the amplitude over the left side was significantly increased. The change over the left ventricle is attributed to the increased work of the ventricle due to augmentation of blood flow through the shunt to the left side of the heart. The absence of increase in amplitude over the left atrium is not comparable from the haemodynami aspect

The relative heart volume showed after shunt operations a mean increase of 71 1 ± 6.8 ml. Confidence intervals on the 99 % level were found at 54 and 90 ml As regards increase in relative heart volume there was no difference between younger and older patients, even when length of observation time was taken into consideration As compared with the values for different age groups in th healthy children studied by Carlgren & Eek the relative heart volume in the author s cases generally was less before operation. After oper tion the values in th uthor patients were significantly higher than the values for healthy subjects of corresponding age. Moderat increase in relative heart volume was thus demonstrated after shunt oper tions for morbus caeruleus.

Angiocardiography was performed before operation in 147 cases. At follow up examination angiocardiography with *injection of contrast medium through the heart catheter (selective angiocardiography)* could be performed or was regarded as permissible in 63 cases. In 37 of these cases patency of the anastomosis was directly demonstrated. The condition in such cases, and also in the cases in which patency was not demonstrated, is discussed.

The follow up study thus showed *encouraging results from shunt operations. From this it is inferred that shunt operations* are justifiable in cases of the tetralogy of Fallot or tricuspid atresia in which for various reasons radical correction is not feasible.

In Honour of Curt Gyllenswärd at his Retirement from the Professorship of Paediatrics at Karolinska Institutet June 30 1962

Edited by ARVID WALLGREN *in collaboration with* C. G. BERGSTRAND SVEN AHNSJÖ *and* NILS ENGSTRÖM

(*Supplement 135*)

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From the Children's Hospital Samariten (Head L. Ström), the Hospital for Infectious Diseases (Head: J Ström) and the Virological Department (Head. A. Svedmyr) of the Central Bacteriological Laboratory Stockholm, Sweden

Adenovirus Neutralizing Antibodies in Swedish Children[1]

by GÖRAN STERNER and GUNVOR SVARTZ-MALMBERG

Adenoviruses have been divided into endemic and epidemic types. The former include types 1, 2 and 5 which have been isolated from children chiefly in the first years of life [2, 6]. Among Swedish children hospitalized for acute respiratory illness a peak incidence of some 10% for these types of adenovirus was reached between 6 months and 1 year of age [12]. These infections were scattered throughout the year. Types 3 and 7, on the other hand, have mainly been discovered in epidemic outbreaks of acute respiratory illness, often associated with gastroenteritis [1, 5, 7, 8, 11]. On such occasions infections were common in higher age groups.

Against this background, it was considered to be of interest to survey the occurrence of neutralizing antibodies to types 1, 3, 5 and 7 in sera from Swedish children free from signs of infectious disease.

Materials and Methods

Sera were collected during the period Sept. 18th–Oct. 5th 1961 from 209 children living in the southern part of the city of Stockholm. One group consisted of 109 children born in 1958–1961 (1–3 years old) and the other group of 100 children born in 1949–1951 (9–12 years old). Of the children aged 1–3 years 91 were examined at 5 different Child Health Centers and the remaining 18 children were seen at the Children's Hospital Samariten. The older children attended elementary schools serving the same residential areas as the Child Health Centers. *All children were free from symptoms of infectious disease when the blood specimens were drawn.* The sex and age distribution is given below

	Preschool children			School children			
Sex	62 boys	47 girls		61 boys,	39 girls		
Age in years	1	2	3	9	10	11	12
Number of cases	53	49	7	7	23	30	36

Owing to the small amount of sera obtained in some cases the number of specimens that could be tested against all five adenovirus types included in this investigation was reduced to 177.

In March 1962, sera were also collected from 16 cases (aged 6–33 years) in whom infection with adenovirus type had been diagnosed 1–6 years earlier by virus isolation and demonstration of a titer rise of complement fixing antibodies. These sera were tested for antibodies against type only.

Neutralization test. The incubation-time technique of Kjellén *et al.* [6] was employed. Only neutralization by serum inactivated at 56 C for 30 minutes is noted. Serum diluted

[1] This investigation was supported by grants from the Karolinska Institutet and from Alfred Österlund Foundation.

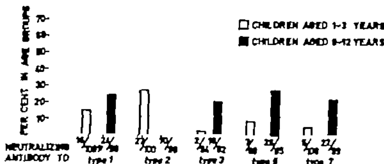


Fig 1 Neutralizing antibodies to adenoviruses types 1 2, 3, 5 and 7 in two different age groups of Stockholm children. Numerator = number of children with antibodies; denominator = number of children tested.

1/* was incubated for one hour at 37°C with equal volumes of virus suspension diluted 1/10. As read after 14 days the titers of the virus suspensions, expressed in log TCD_{50} per ml, were: type 1 7 7 type 2: 7.3, type 3 6.3 type 5: 8.5 and type .9 Of the serum-virus mixture 0.2 ml was inoculated into duplicate roller tube cultures of HeLa cells. Cultures were inspected daily for one week. The result of the neutralization test was recorded as positive if the tubes containing serum did not show cytopathic changes earlier than at least two days after the appearance of such changes in the virus control.

Results

The distribution of antibodies according to age and adenovirus type is illustrated in Fig 1 Among the young children antibodies to types 1 and 2 are the most common, whereas antibodies to types 3 and 7 are much less frequent those to type 5 staying in between. In the older age group type 2 antibodies are present in a significantly higher frequency than any of the other types. If this group is further divided into children 10 11 and 12 years of age the frequencies of type 2 antibodies are closely similar indicating that the conversions take place mainly before 10 years of age As it is known [11] that adenovirus type 7 was prevalent during the autumn of 1950 in those parts of Stockholm where the children of this study live it is of interest to note that antibodies to this type do not occur more frequently than to the other types tested. However no children

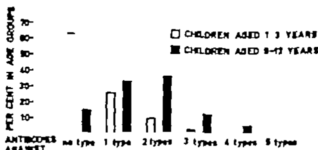


Fig 2 The occurrence of antibodies to one or more of five adenovirus types in 17 children (86 aged 1–3 years, 91 aged 9–12 years)

born after the epidemic showed serological evidence of this infection.

In Fig. 2 the presence of antibodies in 177 sera tested against all five types is shown. Antibodies to one or more of the tested types were demonstrated in 37 % of the young children and in 85 % of the older children. There was no coincidence between antibodies to any particular types that might suggest a heterotypic antibody response.

Of the 16 sera from cases known to have had an adenovirus type 7 infection earlier two were collected from individuals who had this infection in 1955 In both these sera type 7 neutralizing antibodies were demonstrated. The remaining 14 cases had been diagnosed during the out break of type 7 infections in 1959 and of them all but one were shown to have neutralizing antibodies in the specimen obtained in 1962

Discussion

The prevalence of denovirus type 2 antibodies in both ge groups is in ac cordance with the findings of other authors [3, 4 9 13]. The high incidence among the older children indicates that infections with this type are very common. As to types 1 and 5 the results are more variable. In some studies antibodies to these types have been found to be bout as frequent as those to type ... In the present material type 1 antibodies rank next after type 2 antibodies, among the young children, whereas in the older age group they were not demonstrated more frequently than those to types 3 5 and

Adenoviruses types 3 and 7 are known to cause epidemic outbreaks. Where ex tensive outbreaks have occurred, the frequency of seropositive individuals may be quite high, as illustrated by the findings after a type 3 epidemic at Kumla Sweden, in 1956 [7]. In Stockholm however type 3 virus has been encountered only occa sionally since the beginning in 1954, of this series of investigations [6 10 11]. The frequency of seropositive children was cor respondingly low in the present Stockholm material.

During the autumn of 1959 adenovirus type 7 was discovered in a great number of patients living in the same region of Stockholm as the children whose sera have now been investigated. On epidemiological grounds, however it was concluded that this outbreak was not very extensive [11]. This would agree with the relatively low frequency of type 7 antibodies found in the present study It does not seem probable that a drop in antibody titer with time has influenced the results very much since with the same technique antibodies were demonstrated in nearly all cases tested ‑6 years after a type 7 infection.

Apparently the rate of infection may vary considerably in different adenovirus epidemics In this connection it should be recalled that adenoviruses m y be ex creted in large amounts and for long periods of time in the stools. They may thus be disseminated in the same ways as enteroviruses In some epidemics involving a large part of a population group like the Kumla outbreak mentioned above contaminated water in swimming places has been suspected [* 5 7]. If on the other hand, other modes of transmission predominat the infection rate may be much lower not approaching that seen in typical irborne infections like influenza and morbilli [11].

The over-all incidence of adenovirus infections seems to be similar in Sweden to that found elsewhere. Of the children investigated 85 % had acquired antibodies to at least one adenovirus type before the age of 10 years.

Summary

The incidence of neutralizing antibodies to adenovirus types 1, 2, 3, 5 and 7 was investigated in sera of Swedish children aged 1–3 years and 9–12 years. All children were free from symptoms of acute respiratory illness when the serum specimens were drawn. Type 2 infections appeared to have been much more common than those of any of the other types. The correlation of type 7 antibodies to a previously observed outbreak of type 7 infections is briefly discussed. Antibodies to one or more of the tested types were demonstrated in 37 % of the young children and in 85 % of the older ones.

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The Children's Hospital Sachsska / Samaritan
Ringvägen 21
Stockholm So.
Sweden

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From the Flensburg Children Hospital, Malmö (Head: P Selander), and Department of Virology (Head: L. Kjellén) Allmänna Sjukhuset Malmö, Sweden

The Occurrence of Adenovirus in Hospitalized Swedish Children[1]

by GÖRAN STERNER and LARS KJELLÉN

In an earlier study the occurrence of adenoviruses in Sweden during 1953–1957 was reported [13]. Adenovirus type 3 was recovered in 1955 during an outbreak of respiratory illnesses in association with gastroenteritis [14] Since that time epidemics of similar diseases caused by adenovirus type 7 have occurred in Sweden [11 20].

Among the children with respiratory illness a few infections with adenovirus types 1 2 or 5 were found [13, 19 20] These patients were generally younger than 3 years of age Because of the few and scattered cases it was not possible to draw any aetiological conclusions.

In the present study we have intended to gain further information on the spread of adenoviruses among children. For this purpose stool specimens of children ad mitted to the Children s Hospital in Malmö Sweden during the course of one year were tested in tissue culture of HeLa cells. Other cytopathic agents than adenovirus isolated during the study have naturally been included.

Materials and Methods

During the period from March 14, 1959 t March 13, 1960, 405 children were admitted to the Children Hospital in Malmö, a city in the south of Sweden with 230,000 inhabi tants. This hospital, the only one for medical care of children in Malmö, has 120 beds. About 50 % of the patients t admission had signs and symptoms of acute illness in the respiratory tract alone or in combination with ther diseases. More than 800 hildren had non-contagious diseases and were free from signs of acut respiratory illness. The remaining patients were treated for conta gious diseases such as pertussis, scarlet fever meningitis and gastroenteritis.

Collection of specimens It was our inten tion to get a first stool specimen from every patient within the first three days after admission. Such specimens were obt ined from 1022 out of 405 patients. If the first stool specimen was collected later than the third day it was discarded. A seen in Table I the number of cases from which stool spe cimens were obtained at admission varied from about 50–90 % of the total admissions during the year Withi the various ge groups of patients it kept between 0–90 %, however (Table 3) As seen in T bles 1 and 4 there was no obvious selection of patients within certain clinical entities From patient hospitalized for any longer period of time new stool specimens were collected t in tervals of from one to three weeks. More than one specimen was thus tested in 293 children.

The stool specimens were stored t 20°C before testing.

Tissue culture methods Roller tube cul tures of H La cells were employed. For out growth medium of 20 human serum in Parker 199 was used. Before inoculation the

[1] This study was supported by grant from Alfred Österlund' Foundation.

TABLE 1 *Number of cases investigated at admission and per cent of tested cases to total admissions in different clinical entities Distribution by month of study*

Month	Acute respiratory illness		Other contagious diseases		Non-contagious diseases	
	No. of cases	% total admissions	No. of cases	% total admissions	No. of cases	% total admissions
1959						
March	58	82	17	89	31	74
April	60	45	5	46	69	90
May	58	54	14	78	85	80
June	73	60	21	84	56	76
July	58	82	23	59	43	73
Aug.	76	90	25	69	60	78
Sep.	103	93	25	89	52	79
Oct	104	93	12	97	53	84
Nov	114	91	16	84	59	80
Dec	118	93	8	80	51	76
1960						
Jan.	87	93	14	100	65	83
Feb.	104	92	18	94	62	76
March	70	58	8	73	12	46
Total	1 093	82	213	86	617	75

tubes were washed three times with phosphat buffer solution (PBS) The cultures were held in roller drums at 36°C and maintained on bovine amniotic fluid with the addition of antibiotics.

Virus isolations A 10% suspension in phosphate buffer containing 500 IU penicillin and 500 µg streptomycin per ml was prepared by shaking the material in a centrifuge tube containing glass beads. The suspensions were centrifuged at 3500 r.p.m. for 30 minutes and 0 1 ml of the supernatant inoculated into each of two culture tubes. The cultures were inspected twice weekly for at least two weeks.

Hyperimmune sera Sera against the first seven types of adenovirus were prepared in rabbits. The antisera against poliovirus types 1 2 and 3 as well as sera against Coxsackie virus types B1–5 A9 were kindly supplied by the National Foundation, New York.

Neutralization tests The neutralization test against the adenoviruses were performed in accordance with the technique given earlier [13]. Tests against the enteroviruses to be reported were performed according to standard methods as recommended by the National Foundation.

Results

Virus isolations Out of the 1023 first stool specimens a total of 122 (12 %) yielded cytopathic agents (Table 2)

Among these 122 agents were 70 adenoviruses 40 Coxsackie viruses and 12 polioviruses Types 1 2 and 5 dominated among adenoviruses. No type 3 strains were recovered. In two cases the cytopathic agent was neutralized by two antisera against adenoviruses one by types 1 and 5 and the other by types 1 and 7 These agents have not been further investigated. It might be mentioned however that the former agent has been recovered from specimen collected from a boy whose sister at the same time excreted adenovirus type 5

TABLE 2 *Monthly admission of cases which excreted viruses in their stools*

	Adenovirus types							Poliovirus types		Coxsackie virus types		Investigated	
Month	1	2	4	5	6	7	?	1	3	B3	B4	No. of cases	% total admissions
1959													
March	2	5	1	2								108	60
April	1	2		2	1	1			4			134	61
May	3				1							107	55
June	1	4		4		1	1		1			150	78
July	1	2[d]		1	1							134	60
Aug.						1	1			10		151	86
Sep.		1							2	11	1	180	88
Oct.	2	2		1						3	6	278	91
Nov	3[a]	5						1			4	180	87
Dec.	5[b]	1		1				1			3	177	87
1960													
Jan.	4[c]	1										156	90
Feb.	2	1						1				171	87
March												40	66
Total	24	26	1	11	3	3	2	3	9	24	16	1 923	80
				70				12		40			
								122					

[a] One of the cases, admitted once before in October excreted the same type of adenovirus on both occasions.

[b] Two of these strains from the same child admitted to the hospital two times in December.

[c] One of the cases, admitted once before in November excreted the same type of virus on both occasions.

[d] One of the cases, admitted once before in June, excreted the same type of adenovirus on both occasions.

Some of the children were admitted to the hospital more than once during the year From four of these patients the same type of adenovirus was recovered on both occasions. Their admissions were 2 3, 3 and 8 weeks apart respectively From one of the children adenovirus type 2 was isolated in March 1959 and Coxsackie B4 in October of the same year Another child excreted poliovirus type 3 in Sept and adenovirus type 5 one month later

From 295 children more than one specimen were examined. In this group 8 children were positive in their first specimens and six of them were still positive t an examination performed . to 3 weeks later One of them changed type from adenovirus type 7 to adenovirus type 5. The remaining 287 hildren of this group were all negative in their first stools After 1? days to 10 weeks 13 of these patients excreted virus of which 10 were classified as adenoviruses types 1 2 and 5, two as Coxsackie viruses B3 and one as poliovirus type 3

Cl ical pictures Table 4 presented a rough classification of all patients admitted. It might be mentioned that the

TABLE 3 *Age distribution in the main groups of clinical entities investigated and findings of adenovirus types 1 2 and 5 at admission*

Age	Acute respiratory illness Tested	Acute respiratory illness Adenovirus types 1 2, 5	Other contagious diseases Tested	Other contagious diseases Adenovirus types 1, .. 5	Various non-contagious diseases Tested	Various non-contagious diseases Adenovirus types 1 2, 5	Investigated No. of cases	Investigated .. total admissions
Months								
0–..99*	67		45		14	1	326	78
3–5.99*	138	8	30	2a	39	3	207	91
6–11.99*	*09	22a b	36		37		273	83
Years								
1 ..99*	415	22	54		60		529	83
2–6.99*	175	4	29		76		280	2
7 16.99*	89		19		*01		309	3
T tal	1 093	56	213	2	617	3	1 923	80

Two children admitted t the hospital twice ereted on both occasions the same type of adenovirus.

One patient was admitted two months before (4 months old) t the hospital with bronchiti On both occasions adenovirus type 1 was isolated.

One strain excreted from patient who had been admitted 3 weeks before with acut respira tory illness. On that occasion the same type of virus was isolated.

assignment to a diagnostic category was made before the final results of the virological investigation were available

All cases who had shown signs of acute illness in the respiratory tract at admission, were brought together in a large group of "acute respiratory illness" whether this disease was the reason for hospital ization or not As usual in acute respira tory illness symptoms and clinical find ings were seldom restricted to any special part of the respiratory tract but several regions were affected at the same time Therefore and because X ray of chest and sinuses were not always performed, we considered it inaccurate to divide the group of acute respiratory illness" for example in cases with rhinitis, sinusitis bronchitis with or without bronchopneu monia However all forms of acute respir atory illness are represented from simple rhinitis to severe bronchopneumonia The cases with acute respiratory illness were separated into those with and those without gastroenteritis in order to permit a comparison in this respect with earlier outbreaks of adenovirus types 3 and 7 in fections [1 14 20].

More than 800 children were free from signs of acute respiratory illness at admis sion and suffered from various non-con tagious diseases The remaining patient were ill with such diseases as pertussis, scarlet fever mononucleosis, meningitis and gastroenteritis.

From Table 4 it might be observed that in specimens obtained at admission there is an accumulation of virus findings in the group of acute respiratory illness This seems to apply irrespective of virus type Adenoviruses are found in 5 0 among this group of children but only n 0 6 in

TABLE 4. *Virological findings in stool specimens from 1923 cases at admission to the Children's Hospital, Malmö, Sweden, from March 14th 1959 to March 13th 1960*

Type of illness	Number of cases: Total	Number of cases: Investigated	Virus isolated from stools: Adenovirus	Virus isolated from stools: Coxsackie virus	Virus isolated from stools: Poliovirus
Acute respiratory illness without gastroenteritis	1 278	1 037	61* − 5.9 %	27	8
Acute respiratory illness with gastroenteritis	60	56	3 − 5.4 %	2	1
Gastroenteritis without acute respiratory illness	120	111	2† − 1.8 %	1	
Salmonellosis	10	9			
Moniliasis	5	5			
Stomatogingivitis ac.	21	18		1	
Stomatitis membranacea	19	17			
Mononucleosis	7	6			
Exanthema subitum	18	17			
Parotitis epid.	3	2			
Varicellae	1				
Hepatitis inf.	1	1			
Pertussis	9	9			
Scarlatina	1	1		1	
Tubercul. pulm.	1	1			
Meningitis purulenta	13	6			
Meningitis serosa	6	6			
Meningitis serosa cum paresis Encephalitis		2		1	1
Various non-contagious diseases	816	617	4 − 0.6	7	2
Total	2 406	1 923	70	40	12

* From three children admitted to the hospital more than once during the study the same type of adenovirus was recovered at both occasions.

† One of these cases had been admitted to the hospital 3 weeks before with acute respiratory illness. The same type of adenovirus was excreted at both admissions.

the group of various non-contagious diseases. The difference by X^2 test is highly (**) significant.

It might furthermore be observed that none of the nine patients from whom poliovirus type 3 was recovered were diagnosed as clinical poliomyelitis, while one of the three children, who excreted poliovirus type 1 had paralytic poliomyelitis. The other paralytic cases in the material excreted Coxsackie virus B3.

Epidemiological remarks. During the year under study no obvious epidemics of characteristic clinical entities were seen in the city of Malmö except a moderate increase during February and March 1960 of respiratory illnesses clinically diagnosed influenza. Only a few of these cases were however serologically verified as influenza. No other outbreaks of presumed viral genesis were known.

It can be seen from Table 2 that cases from which adenoviruses were recovered are distributed all over the year with the frequency of isolations lowest in August and September 1959. On the other hand it might be seen that the polio- and

TABLE 5 *Age distribution in 135 cases harbouring viruses in their stools*

Virus isolated at admission from 122 cases. From 13 cases with negative findings at admission, virus was excreted later on during the hospitalization (these cases are put in a parenthesis).

Virus strains	Months			Years			Total
	0–2.99	3–5.99	6–11.99	1–2.99	3–6.99	7–16.99	
Adenovirus							
Type 1		2[b] (1)	9[b,d] (_)	10	2[e]		4 (2)
2	1 (1)	7[c] (1)	10 (2)	7 (2)	1		[illegible]6 (4)
4						1	1
5	(1)	2	3	5	1		11 (1)
6			1				3
7			1	1		1	3
Not yet typed							2
Coxsackie virus							
B 3		3	3	7	5 (2)	6	24 (2)
B 4		2		12			16
Poliovirus							
Type 1	1		1	1			3
3	(1)[a]	2		3			9 (1)
Total	(3)	18 (2)	2_ (4)	48 (2)	1_ (2)	10	12_ (12)

[a] Newborn admitted from maternity ward
[b] One strain from patient admitted twice to the hospital, 4 and 6 months old respectively
[c] Two strains from the same patient, admitted to the hospital more than once
[d] Two children admitted twice t the hospital excreted on both occasions adenovirus type 1
[e] The children were three years old.

Coxsackie viruses appeared during limited parts of the year. Most of the poliovirus type 3 isolations occurred in the spring while Coxsackie viruses dominated among enterovirus isolations in the autumn.

Table 5 reveals that 90 % of the adenovirus excreters were less than three years of age, 50 % being below one year. During the latter half of the first year of age the incidence of adenovirus type 1, 2 or 5 excreters reached 10 % among the children with respiratory illness (Table 3).

The age distribution of enterovirus excreters was somewhat similar to that of adenovirus excreters (80 % below 3 years of age, 30 % below one year).

Among the virus excreters 25 children attended 6 different day nurseries and one lived in an orphanage. In the former group 16 harboured adenoviruses, 5 Coxsackie viruses, 3 polioviruses and one poliovirus in Sep. and adenovirus one month later. Only a few of the patients with viruses in their stools were siblings. Fig. 1 shows the living places for the children harbouring viruses at admission. A statistical analysis with X^2 test gives highly significant(**) evidence that children in age 0–4.99 years were more often admitted to the hospital from some districts in Malmö than from others, independent of total number of children in these ages living there. The former districts are mainly inhabited by people whose social standard makes hospital care probably more urgent. In the abovementioned age group, however, the findings of adenovirus types 1, 2 and 5 from children with acute respiratory illness seems to be the same in all districts of the city.

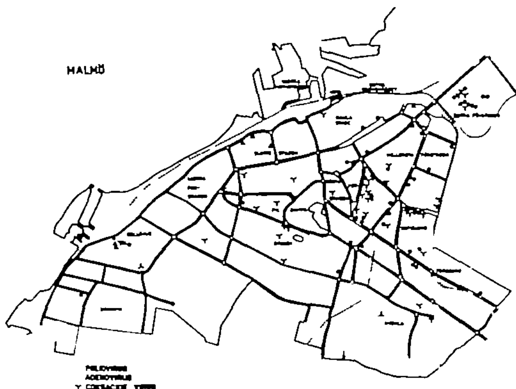


Fig 1. A map of Malmö, Sweden, showing the living places of children excreting viruses on admission to the Flensburg Children Hospital.

It may be mentioned in this connection that the cases with polio type 3 lived in different parts of the town and no obvious connection between the cases was found. On the other hand the poliovirus type 1 exere ters lived in the same part of the town and two were brothers.

The 13 patients with negative stool findings on admission but from whom viruses were isolated later on, might have acquired their gents in the hospital. With only one exception, they were treated in the same wards and imultaneously with patients known to exeret the same virus type somewhat earlier The 10 children with adenovirus in later stool spe eimens all had more or less signs of a nosocomial respiratory illness. Yet the possibility remains that the adenovirus infection was contracted before hospitalization and had no relationship to the nosocomial illness. Some types of adenoviru are found in high per cent in tonsils and adenoid [6 8 16 1]. Probably as a result of this persistence in the mentioned organs adenovirus types 1 and 2 occasionally are excre ted at sporadic i tervals, months fter an initial infection [18]

Discu ion

More than a half of an ordinary pedi atric clientele admitted to a children hospital over a period of one year con sisted of patients with acute respiratory illness the aetiology of which in most cases

remained unknown. Such ailments usually do not provide problems to the medical staff and the fact that the children in the majority of instances make rapid recoveries tends to lessen the interest in our most common diseases. As soon as we recognize that repeated minor infections might not be harmless or that they become an econonomical problem the need to do something about it becomes more urgent. Knowledge of the occurrence of potential pathogenic agents (viruses and bacteria) causing respiratory illness can give us possibility of bringing them under control. Several new groups of viruses have in the last years been associated with acute respiratory illness in children [3, 4]. Our own interest since 1954 [1, 13, 19, 20] has been to gain information on the part played by the adenoviruses in acute infections of the respiratory tract in children. Evidence in Sweden has been brought forth that adenovirus types 3 and 7 are to be found during outbreaks of acute respiratory diseases often characterized by rather typical symptoms [1, 11, 13, 20].

The present study reveals that among children suffering from acute respiratory illness adenovirus are to be found in 5.9 % but in only 0.6 % in a group of non-contagious diseases. Most of the adenoviruses (56 of 64 strains) in the former group belonged to types 1, 2 or 5. The findings suggest that these infections may cause acute respiratory illness although the children might be excreters for rather long periods of time [13]. Experience with adenovirus types 1, 2 and 5 is evidently early in life in Sweden as in other countries [9, 10, 16]. It is interesting to note that adenovirus findings of types 1, 2 and 5 were recovered throughout the year. No strains of adenovirus type 3 and only a few of type 7 were encountered. This observation is in line with earlier findings that adenovirus 1, 2 and 5 infections are endemic [16] while type 3 and 7 viruses tend to cause epidemic outbreaks of acute respiratory illness [2, 15] often associated with gastroenteritis [5, 7, 11, 14, 20, 21].

The fact that of enteroviruses only Coxsackie B virus and a few polioviruses but no ECHO virus were recovered may very well be due to the use of HeLa cells exclusively for virus isolation. Again most of the excreters suffered from acute illness in the respiratory tract.

Summary

The occurrence of adenoviruses in stools collected from 1923 cases at admission to the Children's Hospital in Malmö, Sweden, has been followed during the course of one year. In 6.3 % cytopathic agents were isolated. The material has been classified in two main groups: children with signs of "acute respiratory illness" at admission and those with "various non-contagious diseases". In the former group adenovirus was recovered from 5.9 % against 0.6 % in the latter group. The isolated adenovirus belonged to types 1, 2 and 5 mainly, only a few to types 4, 6 and 7. Adenovirus types 1, 2 and 5 were found in the ages from 3 months to 3 years, half of them below one year. These findings were distributed throughout the year of observation. Probably nosocomial infection with adenovirus types 1, 2 or 5 was seen in a few cases.

Most of the children excreting enteroviruses such as Coxsackie virus types B3 and B4 and poliovirus types 1 and 3 also had signs and symptoms of acute respiratory illness.

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From the Surgical Department of the Pediatric Clinic Karolinska Sjukhuset, Stockholm, Sweden

Essential Hematuria in Children—Prognostic Aspects

by ALEXANDER LIVADITIS and N O ERICSSON

Hematuria is a condition calling for immediate investigation to ascertain the underlying etiologic factor In many instances, however the cause of bleeding cannot be determined despite intensive examinations. These unexplained hematurias constitute a separate group and are generally defined as "essential hematuria" This designation does not imply a definite disease but probably represents a sort of melting pot including hematurias of multiple pathogeneses Silva de Assis [12] defines essential hematuria as renal hematuria, uni- or bilateral, intermittent or continuous and more or less intense without any evidence of histologic or functional alterations of the kidneys. The lack of detectable changes has led to different etiological hypotheses and a wide variety of nomenclature The synonyms which have been proposed such as local renal hemophilia constitutional renal hemophilia angioneurotic renal hematuria renal epistaxis, hematuria of small foci hematuric renal nephralgia represent attempts to define a condition with an obscure etiology Failure to recognize the true causative factor is mainly due to the present-day diagnostic inadequacy Only histologic studies might give clues to diagnosis. In most instances, however hematuria is not severe enough to warrant nephrectomy But even after removal of the kidney in extreme cases, examination of the specimen has failed to reveal characteristic lesions.

It is evident that, in the individual case our diagnostic possibilities are limited. This makes obvious the need to collect more statistical material, both clinical and experimental, in order to acquire a better knowledge of this condition.

Comprehensive series of essential hematuria in children have not yet been reported. Hematuria however may become a challenging medical problem and a cause of deep parental concern At the sight of bloody urine the parents become upset and anxiously demand some form of energetic treatment. They are impatient to know how dangerous the condition may be and what its ultimate outlook is Even doctors may be in doubt whether restrictions or treatment are required

In an attempt to study the prognosis within a reasonable period we have followed up 50 children with essential hematuria to whom no restrictions and no treatment have been given

Material

During the period 1952 to 1960 30 males and 20 females with essential hematuria were admitted to the Surgical Dept of the Pedia

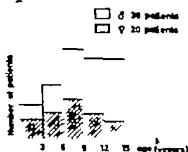


Fig. 1. Age and sex distribution in 50 patients with essential hematuria.

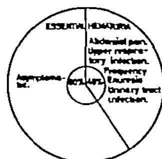


Fig. 2. Associated clinical manifestations in 50 patients with essential hematuria.

tric Clinic of Karolinska Sjukhuset. Their age ranged from 1 to 15 years (Fig. 1). The initial hematuria was macroscopic in 36 and microscopic in the remaining 14 patients. The duration of macroscopic hematuria prior to admission varied from some hours to two days. The average duration of microscopic hematuria prior to admission was one year.

Abdominal pain was present in eight patients, upper respiratory infection in 7 and frequency with burning on micturition in two. Two other patients suffered from enuresis. Urinary tract infection was encountered only once. In the remaining 30 patients hematuria was the only presenting symptom (Fig. 2).

The diagnostic procedures included urinalyses, both during bed rest and activity, Addis count, urine culture and sensitivity tests, guinea pig test, sedimentation rate, blood pressure determinations, antistreptolysin levels, intravenous pyelograms, micturition urethrocystograms, cystoscopy with catheterization of the ureters, renal function tests, bleeding and coagulation tests, excretion of calcium in the urine and blood chemistries, especially serum calcium and phosphorus values.

Urographic studies showed in one case horseshoe kidney, in two cases unilateral renal aplasia, in two cases duplication of the ureters and in one additional case unilateral hydronephrosis (Table 1). These findings were considered incidental, deprived of any causative importance.

In nine patients it was possible to determine the side of bleeding. The left side was involved in three patients, the right side in one patient and both sides in five patients.

Because of the mild character of bleeding no nephrectomy was indicated in any case. Two patients presenting urethral polyps were subjected to polypectomy. Two others with signs of cystitis were treated medically. Apparently these lesions had no causative significance since hematuria continued after successful treatment of these local conditions. No restrictions were prescribed to our patients. They were allowed to attend school, indulge in athletics and generally to assume a normal life. None of these children received any kind of specific treatment.

Results of the Follow-up Study

The present follow-up was partly carried out by correspondence. No information was available in four patients. In the remaining 46 patients the follow-up time

Table 1. *Roentgenographic findings in 50 patients with essential hematuria*

Finding	No.
None	44
Horseshoe kidney	1
Absence of one kidney	2
Ureteral duplication	2
Hydronephrosis	1

varied from 4 months to 9 years. In 40 patients (=87 %) the follow up time was more than 2 years, in the remaining 6 (=13 %) less than 2 years. The average follow up time was approximately 4 years At the time of investigation 36 patients were well and had no further hematuria. Two still had occasional microscopic hematuria Two others had macroscopic hematuria only once after discharge The remaining six had recurrent macroscopic hematuria. All patients with recurrent hematuria were repeatedly investigated in our clinic or elsewhere In no case was any serious disease such as glomerulonephritis or tumor discovered. The persistence of hematuria did not seem to affect the patients general condition. They attend school and indulge in normal activities. No growth disturbances or anemia have been noted

Discussion

Essential hematuria is a diagnosis by exclusion While this diagnosis is inadequate from an etiological point of view it may be helpful in the evaluation of prognosis. In the pediatric age group acute nephritis, neoplasm and urinary tract infection are commonly recognized causes of bleeding The diagnosis of these conditions is usually readily established after thorough examination of the patient.

Less common causes of hematuria have been identified and each of them deserves special consideration The association of hematuria to hereditary hemorrhagic telangiectasia has been discussed by Campbell Jr [9] Hemangiomatous lesions of the urinary tract producing hematuria have been described by Bloch [1] and Webb-Johnson & Warwick [15] Hematuria due to degenerative changes of the vessel walls as a manifestation of localized collagen disorder has been described in recent years [13] Familial occurrence of hematuria due to genetic abnormality has been reported by Russell & Smith [11]. Animal experimentation has shown that vasomotor disturbances following neurovegetative stimuli may produce hematuria [5 9 12, 14] This led some authors to carry out kidney denervation or autonomic nerve blocking in the treatment of some cases [4 7] These conditions, however have limited significance in clinical practice because they are very rare Moreover some of them can be recognized on the basis of their clinical or roentgenographic features. It is well to stress at this point that while hemangiomata are a common lesion in childhood their incidence in the urinary tract is extremely rare Roentgenographic evidence of intrapelvic hemangioma is possible provided the lesion is sizable Hereditary telangiectatic lesions of the urinary tract may be suspected from the associated clinical manifestation of the disease

While there is general agreement that essential hematuria is not an autonomous disease the topographic location of the lesions is a matter of debate However there is a tendency in the literature to consider the calico-papillary junction as the commonest site of bleeding The mechanism of bleeding is believed to be hemorrhage from the caliceal vein into the renal pelvis through the establishment of a pyelo-venous communication [3 6 8].

It is possible that improvement of diagnostic methods in the future will permit the detection of variable minute lesions responsible for bleeding Aortography

which has been introduced by some [10] as an auxiliary diagnostic procedure in adults has no place in the investigation of hematuria in children. In young subjects, conventional methods are often sufficient to settle the diagnosis without resorting to aortography which is not free from danger. Emphasis should be placed on the value of cystoscopy while gross hematuria is present. This kind of "emergency" cystoscopy provides the opportunity of localizing the site of bleeding.

The limited experience recorded in the literature and the limited nature of our observations make it impossible to give any definite statement regarding ultimate prognosis in children with essential hematuria. On the basis of our observations, however it seems probable that the disease, with the definition given, has a benign course and is not uncommon in children.

From a practical standpoint, if no cause of bleeding is found after thorough investigation and if after a reasonable period of observation there are no recurrences, the prognosis should be considered good. Persistent hematuria however must be considered more serious and demands repeated investigation with the thought of some lurking pathology in mind. If acute nephritis is definitely excluded we do not see why these children should be placed on bed rest or other restrictions.

Summary

Essential hematuria is a collective term including hematurias of unknown etiology. In reviewing the literature we were impressed by the paucity of contributions concerning the significance of essential hematuria in children. To gain some prognostic information, a follow-up investigation of 50 children with essential hematuria has been made. No treatment whatsoever was administered. The average follow-up time is approximately 4 years. Thirty-six of the patients were found to be completely healthy. Ten still had occasional macroscopic or microscopic hematuria. In the remaining four no information was available. No growth disturbances, anemia or morbid manifestations of any kind have been observed. The lack of comparable series makes it difficult to give any definite statement concerning long term prognosis. In our material however the disease revealed a benign course suggestive of a good prognosis.

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Department of Surgery
Pediatric Clinic
Karolinska sjukhuset
Stockholm 60
Sweden

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From the Pediatric Clinic, University Hospital, Uppsala

The Pattern of Blood Disorders in Swedish Children

An Analysis of a Clinical Material from a 10 Year Period

by A. CHAKRAVARTHY[1] and B. VAHLQUIST

Patterns of disease in childhood vary greatly in different regions, and this is also the case to a great extent in hematological conditions. In comparing Scandinavia with African countries and India it is found that both the type and frequency of blood diseases are very different This is particularly marked with the anemias. In Scandinavia anemia due to hemoglobinopathy is rare while such conditions are very common in many regions of Africa India appears to occupy a middle position. In Scandinavia anemias due to dietary deficiency or infection have progressively diminished during the last few decades while anemias from these causes, or due to parasitosis, are still a problem of first magnitude in many African countries and in India deserving the greatest attention from the preventive health services. The frequency of blood diseases in childhood is consequently many times greater both in African countries and India than in Scandinavia.

The situation cannot however be generalized to include all types of blood diseases. The incidence of the leukemias, for example, is probably just as high in Scandinavia as in the other regions, and as regards anemias in the newborn due to isoimmunization, the frequency is considerably higher in this part of the world because of the relatively high frequency of Rh-negative individuals.

A brief account will be made below of cases with hematological disorders who were treated as in patients at the Pediatric Clinic in Uppsala during the 10-year period from 1951 to 1960 This clinic is the only specialized one of its kind in Uppsala county and serves an area with about 200 000 inhabitants of whom about 45,000 are between the ages of 0–15 years. It should be noted that as a rule the number of beds is adequate so that refusals are never necessary even for uncomplicated anemias of the iron deficiency type The University Hospital of Uppsala also serves as a regional hospital for a population of about 1.3 million and apart from patients in the area first mentioned, patients transferred from other provinces for investigations are also accepted. These latter represent a selected material and of course also the material from our own province is in a way selected, namely with regard to the degree of severity

The population served by the hospital is small compared with the situation in many other hospitals not least in Africa and India The size of the material is also modest but even so it may give an idea of the fre-

[1] Erlander fellow in pediatrics. Present address Medical School, Nagpur India.

TABLE 1 *The number of children hospitalized for different hematological disorders at the Pediatric Clinic Uppsala during the 10-year period 1951–60*

Diagnosis	Sex ♂	Sex ♀	Region Uppsala county	Region Other counties	Total	Calculated risk of contracting disease before 15 years of age *
Anemias						
Iron deficiency	81	38	110	9	119	[> 0.37]
Megaloblastic	2	2	2		4	0.007
Hemolytic total	137	90	90	137	227	0.30
Intrinsic defect						
Microspherocytosis	9	3	3	9	1	0.01
Hemoglobinopathy	2	0	0		2	—
Extrinsic defect						
Isoimmunization (Rh)[a]	123	83	84	122	206	0.23
Auto-immune	1	4		3	5	0.007
Others	2	0	1	1	2	0.003
Aplastic						
Panmyelophthisis	5		1	6	7	0.003
Others	2	1	1		3	0.003
Secondary (infection, malignancy etc.)	52	39	84	7	91	[> 0.28
Agranulocytosis	2	4	1	5	6	0.003
Leukemia						
Acute	10	16	13	21	34	0.04
Chronic	4	0	3	1	4	0.01
Thrombocytopenia						
Idiopathic	14	13	17	10	27	0.06
Others	1	8	7		9	0.02
Hemophilia						
A	13			13	15	0.007
B	1	1	0		2	—
Other types	1	1	0	2	2	—

[a] Cases of ABO-isoimmunization are not included. A sampling from 1956–67 indicates the frequency of *fra k hemolysis* due t this cause t correspond to bout three cases per year e.g. about 0 10%.

quency and distribution of different types of hematological disease conditions. It may also be claimed that the diagnoses are fairly accurate since hematological research has been one of the chief interests at the clinic for many years

An account of the whole material is given below and this is f llowed by a somewhat more detailed analysis of the material of iron deficiency anemia

I Survey of the Entire Hematological Material

The fact that the Pediatric Clinic in Uppsala is the only one of its kind in the county and the immediate population served is thus relatively well demarcated, renders it possible to carry out certain *frequency calculations* Table 1 shows the patients from Uppsala county (including

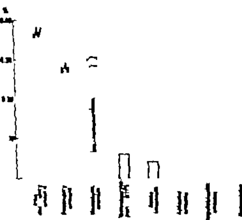


Fig 1 Calculated risk of contracting certain hematological disorders between birth and 15 years of age (the Uppsala material from 1951–60).

also a small, adjacent part of Stockholm county) on one hand and from other counties on the other The values given in the frequency column are based on the relation between the number of cases of certain diseases from Uppsala county and the total childhood population for this area, calculated to an average of about 45,000 for the 10-year period. It may be assumed that for certain diseases all cases are included (g. leukemia, aplastic anemia, Rh-disease and thrombocytopenia) For others again it is obvious that the cases observed at the clinic constitute only a part of the total, and in the main a selection of the more severe cases. For these the frequency figures are given in parenthesis and are marked to indicate that they are to be regarded a too low It is true in fact, of many of the disease categories that the representation is so limited that the frequency figures must be very uncertain. They have been reported nevertheless in order to give an idea of the order of size

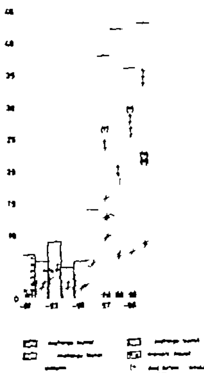


Fig 2 The material of isoimmunization (Rh) at the Pediatric Clinic Uppsala, 1951–60 (Bjöln [9]).

In Fig 1 the frequency figures for some of the commonly occurring blood diseases have been arranged diagrammatically The first two places are occupied, as could be expected, by *iron deficiency anemia* and by *secondary anemia* (due to infection, malignancy acut blood loss etc) In the third place are found cases of *isoimmunization due to Rh-incompatibility* Since 1956 Uppsala has served as a treatment center for this category of children from four different counties corresponding to a population of bout one million. The Rh group of all expectant mothers is determined, and the Rh negative mothers are exam ned for possible immunization. It is

very uncommon for children with Rh disease to be born without this being known beforehand. Treatment with exchange transfusion is performed in about 70 % of the cases and can, when indicated, be commenced almost without exception during the first hours of life.

The total number of newborn with Rh disease treated at the Pediatric Clinic between 1951 and 1960 is 206. The mortality for this group was in all 4.8 %, but if cases of death of other causes were eliminated the "true mortality" in Rh diseases was 3.0 %. Other data concerning treatment etc. may be seen in Fig. * (Sjölin [9]).

Other types of hemolytic anemias are comparatively few (for details see Table 1). Only two cases of *hemoglobinopathy* were observed during the 10-year period. These were two siblings with hemoglobin H, who were among the first cases of hemoglobinopathy ever to have been described from the Swedish population [6]. During the last few years isolated cases of hemoglobinopathies of other types have been observed in other parts of Sweden. These are mainly cases with hemoglobin M and also a peculiar familial affection designated as "hereditary benign erythroreticulosis" (Bergström & Jacobsson [1]) with a considerably increased content of hemoglobin F but completely different from thalassemia. Analyses of the hemoglobin types are performed in many clinics in Sweden. Even if cases still are overlooked the scarcity of patients with hemoglobinopathy in Sweden is therefore to all evidence a reality. It should be added here that an examination of the blood from 110 children of Swedish nomad Lapps in no case gave evidence of abnormal hemoglobin as far as zone-electrophoresis goes [8].

Fourth in place comes *acute leukemia*. The frequency of this disease has been stated from many places to have increased during recent years. The present material is much too limited to provide any detailed analysis in this respect. If the frequency figures for Uppsala county are transferred to Sweden in its entirety, this would correspond to ca. 40 cases below 15 years of age annually of all live born ca. 105 000 in Sweden. Since the total mortality is nowadays very low among Swedish children (according to the statistical information in 1959 it was 1.66 % for the age group 0–1 year, on an average 0.08 % for 1–4 years, 0.046 % for 5–9 years and 0.03... for 10–14 years) the significance of leukemia thus has become increasingly great.

The material also includes 4 cases of *chronic granulocytic leukemia*. These cases have been described in detail by Vahlquist & Vallie [14].

Fifth in frequency are the *thrombocytopenias*, the majority of which deserve the designation of idiopathic. A few of these underwent splenectomy and are included in the follow up study of splenectomized children by Broberger, Gyulai & Hirschfelt [*]. The other types of hemorrhagic disorders included do not exhibit any special features which justify further comment in this connection. The group *pseudo-hemophilia* is heterogeneous and includes among others a few cases of suspected Willebrand disease.

The remaining group of blood disorders is low in frequency and rather heterogeneous. The *megaloblastic anemias* are very rare among children in Scandinavia. The

isolated cases included in the material were of the type 'transitory megaloblastic anemia' with no relation to steatorrhoea.

The cases of *aplastic anemia* will be described elsewhere [4]. Of the eleven cases, nine were fatal.

Among the patients with *refractory anemia* one is especially worthy of mention, since this was the first carefully analysed case of disturbed hemoglobin synthesis in a normal hemoglobin type [3].

II. Iron Deficiency Anemia

The frequency of iron deficiency anemia has decreased considerably in Sweden during the last few decades. At the time when the senior author worked on his dissertation on serum iron [13] there were still numerous cases of iron deficiency anemia in children, some of a severe nature but the situation has since changed noticeably. Even if the figure given in Table 1 is definitely too low it nevertheless gives an idea of the incidence which nowadays in Sweden is far below that encountered in many tropical countries.

Our material includes a total of 110 cases placed under the heading of iron deficiency anemia (including anemia resulting from chronic blood loss). Fig. 3 has been based on 32 of these cases. This group represents those patients who underwent more thorough laboratory work up including for example, hematocrit, serum iron and transferrin determinations.

As regards the *age distribution* it may be seen in Fig. 3 that the majority of these patients with iron deficiency anemia are in the first few years of life; this is in spite of the fact that the number of anemic children in higher age groups are certainly more completely represented since the

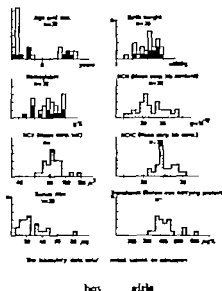


Fig. 3. Various data relating to a selected group of children with iron-deficiency anemia (the Uppsala material from 1951–60)

indications for admission and careful investigation are greater the older the child with iron deficiency anemia. As may be expected, puberty seemingly brings once again a slight rise in the frequency of anemia cases.

Regarding *sex differences*, in both the unselected (Table 1) and the selected (Fig. 3) iron deficiency material there is a marked predominance of boys. The same observation has been made before on large materials [16]. It may in part be explained by the fact that iron deficiency anemia is often found incidentally in patients admitted to hospital for other acute disease conditions. In our total hospital material the ratio of boys: girls is about 1.2: 1.0. Anyhow there is a striking contrast between the situation in children as compared with that in adults, where in Sweden, as in many other countries, 80–90% of the iron deficiency anemia cases are women,

due primarily to the extra strains imposed by menstruation and pregnancy

As regards *birth weight* 6 out of 3* showed values below 2,5 kg In an unselected population in Sweden 4–5 % are born below this weight The high frequency of children with a low birth weight in an iron deficiency material is a regular occurrence e.g 1?6 out of 3 3 children (34 %) in the material of Zurukzogly Sklavounou The incidence of pronounced iron deficiency anemia in children with a low birth weight has, however decreased considerably in Sweden during recent years as a result of preventive iron administration to the premature and a more complete diet including adequate quantities of iron.

Among *laboratory investigations* tests for occult blood in the feces are extremely important even in children Anchylostomiasis does not exist in Sweden but it is not infrequently that the Weber test reveals occult blood losses of other causes, e.g ulcer polypus, Meckel s diverticulum hernia etc In the present material hemorrhage was demonstrated in 25 as a partial or complete cause of anemia. It must be admitted that this percentage figure is probably misleadingly high since children with an anemia due to hemorrhage often show a more intensive or recurrent anemia and they are therefore admitted to hospital for investigation to a greater extent than uncomplicated cases of iron deficiency anemia

As regards blood analyses, certain data are given in Fig 3 Regarding the Hb-values no cases have been included which did not exhibit a Hb of lower than 10 g Regarding Mean Corp Hb Content (MCH) Mean Corp. Volume (MCV) and Mean Corp.Hb Concentration (MCHC) a few cases have obviously been included with such high values that the character of iron deficiency anemia could be questioned (Fig 3) The values given in the figure all refer to the first ones obtained and in such cases later values were often lower This in turn may for MCH and MCV be due to the uncertainty of erythrocyte counting with conventional methods. In 1960 an automatic-electronic device for determination of the number of erythrocytes was introduced at the clinic s routine laboratory this gives more exact values and thus also a much greater degree of certainty for the individual MCV and MCHC values. The lowest values for the whole material were 4.8 g % for Hb 64 μ^3 for MCV and 15 g $\times 10^{-12}$ for MCH This represents a considerable decrease but nevertheless no extreme findings compared with those of other workers It should also be added that cases with a really severe iron deficiency anemia were relatively few in the present material

In determining the diagnosis of iron deficiency analysis of the serum iron and of the transferrin i e the iron-carrying protein fraction in the serum are of great value Both of these analyses were introduced at an early stage at the clinic the serum iron analysis 20 years ago (13) and the transferrin almost 10 years ago (3) The values from the present material are shown in Fig 3. Only untreated cases are included We see the typical picture with a low serum iron and relatively high transferrin which together give a very low degree of transferrin saturation. In those cases where the transferrin was normal or definitely reduced this may be explained by a simultaneously occurring infection

Iron deficiency and iron deficiency anemia are not diseases in themselves but only symptoms. It is thus necessary in every case to attempt to discover the *cause of the iron deficiency*. It has long been known that in the growing individual the following play a role: low birth weight early ligation of the umbilical cord, rapid growth, iron deficient diet and blood losses.

A low birth weight occurs much more often in African countries and in India than in Scandinavia. The number of children with a birth weight below 2500 g, as already mentioned, lies at 4–5 % in Sweden, but in the other regions discussed is often over 20 %. A diet deficient in iron is more often the rule than the exception in childhood in these countries, while where Sweden is concerned it may be said that no child needs to have a deficient diet for reasons of poverty. This of course does not prevent the fact that certain children, because of ignorance or indolence are less well cared for as regards diet. By the preventive work of the child welfare centres, and increasing information to the public regarding dietary questions, however even this is becoming increasingly less common. Chronic loss of blood as a cause of iron deficiency usually in the form of occult intestinal hemorrhage does also occur in Swedish children but is uncommon compared with the tropical countries, where intestinal parasitosis with for example hookworm, is of enormous extent in many places. It is of interest to note in this connection that American workers have recently observed [7] that small losses of blood from the intestine are a relatively common occurrence in severe forms of iron deficiency anemia, even in cases where no definite source of hemorrhage is found in the form of hookworm infection or organic changes in the intestinal wall.

Iron deficiency anemia is a *preventable condition* like rickets scurvy and beriberi. It should be attacked and eradicated with similar methods. In Sweden today with its high standard of living its satisfactory general hygiene and preventive health care it has almost played out its role as a socio-medical problem. This is in sharp contrast to many other countries in the world. It is only in recent years that in the developing countries the frequency and damaging effects of iron deficiency anemia have begun to be appreciated to their full significance [15].

Summary

A report is made of the hematological material from the period 1031–1000 at the Pediatric Clinic in Uppsala. The frequency of different forms of blood diseases is discussed. Special attention is paid to iron deficiency anemia. The investigation emphasizes that the total number of blood diseases among children is low if hemoglobinopathies are uncommon if the standards of living and general hygiene are satisfactory and if the resources for preventive health care are good.

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(BV) Pediatric Clinic
U iversity Hospital
Uppsal
Sweden

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From the Dr Willem van den Berghstichting in Noordwijk (Head, Chr Steketee) and the Department of Pediatrics (Head Prof. Dr G M H. Veeneklaas) of the University Hospital, Leiden, The Netherlands.

Studies in Oligophrenia I

Growth in Mentally Deficient Children

by H H. VAN GELDEREN

Normal growth of a child is provided by several known factors and a number of factors which are still unknown. In the majority of patients with retarded growth the cause of the dwarfism is unknown [10]. Probably mental defectives form the largest group among children with dwarfism and it is obvious to assume a connection between cerebral defect and the growth disturbance

Studies of growth in mental defectives were made as early as 1881 A review of the older literature is given by Davenport & Minogue [1] and Flory [4] However virtually all of these studies were performed to analyse the correlation between the degree of intellectual defect and somatic growth.

In trying to elucidat the relation between growth disturbance and cerebral defect, classification of oligophrenia according to the nature of the cerebral defect is required As a clinical-anatomical division is impossible in view of th poor relation between anatomical defects and etiology [9], we have attempted a classification in which the time at which the injury to the cerebrum occurred plays an important part. In all probability growth is determined by various factors in various phases of development [11] so that classification according to the time of occurrence may serve to reveal correlations

The classification we have used in our study is presented in Table I It may be assumed that serious degrees of mental deficiency are virtually always accompanied by distinct cerebral lesions The last group (5) conveniently called "mild oligophrenia" is composed of children with IQ of 70 or more who have no signs of cerebral defects to peak of Many of them belong to what Yannet [13] has called "marginal population" some of them are only pseudo-retarded children. Their admission to the institution is determined usually by social circumstances. We have included these cases of mild oligophrenia to compare them with the ment l defectives of the same institution.

There have been few studies made in which the growth of mental defectives has been correlated with the etiology Yannet [13] in the U S and Ito [8] in Japan compared prenatally and postnatally injured patients with little result Querido [10] suspected a difference in growth between children injured before birth and those

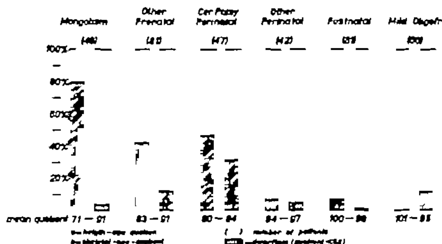


Fig 1

injured after it but sufficient data to prove thi were lacking Dutton [3] is of the opinion that on the basis of differences in growth patterns a group of "metabolic amentia can be distinguished. Just which abnormalities are covered by the term metabolic amentia, is, however not clear

In 550 children aged 3 through 16 years in the institution for the mentally deficient at Noordwijk an attempt was made by means of physical examination, specific histories collection of data concerning earlier hospital investigations etc to arrive at a diagnosis which would enable classification in the previou ly determined diagnostic groups This was possible in 384 patient (70) For the remaining patients either the diagnosis remained in doul t or sufficient data were not available The results are summarized in Table 1 Patients with hypothyreoidism or patients treated with thyreoid were excluded as were also a few cachectic patients and a case of progeria

Physical measurements and skeletal age were determined by the author Height and skeletal age were expressed as percentage of the normal (growth curve of Dutch children compiled by de Haas & de Wijn [7] and the skeletal age atlas by

TABLE 1 *Classification of patients with oligophrenia*

1 Prenatal		144
( ) mongolism	49	
(b) multiple congenital malformations	20	
( ) status dysraphicus	10	
(d) familial microcephaly	4	
( ) rubeola, lues, toxoplasmosis	13	
(f) rare syndromes and others	13	
(g) familial severe oligophrenia	35	
Perinatal		59
( ) with cerebral palsy	31	
(b) without cerebral palsy	4	
( ) kernicterus	16	
3. Phenylketonuria		4
4. Postnatal brain damage		67
5. Mild oligophrenia pseudo-oligophrenia		80
Total		344

Familial, i.e. one or more other cases of oligophrenia among siblings or parents.

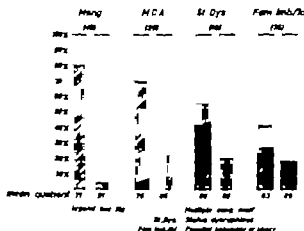


Fig. 2.

Greulich & Pyle [6]) Height-age and skeletal age were expressed in months The "height quotient" and "skeletal age quotient" obtained in this way are given in Tables 2 and 3 and in the figures.

There is a striking and highly significant[1] difference between the growth of patients in the diagnostic groups. Among the children with cerebral lesions of prenatal origin the frequency of dwarfism is high, especially among patients with mongolism and multiple congenital malformations, to a lesser degree also in the other prenatal cases. The growth pattern of these dwarf is usually that of retarded height with much less retardation in skeletal maturation and often with normal sk letal age This pattern has already been described by Dutton [2] for mongols and i also found in so-called primordial dwarfism Growth hormone deficiency or unresponsiveness to this hormone would also produce this type of dwarfism nothing is known however about the role of growth hormone in these patients As far as we know the cerebral lesions in the large majority of these children with prenatal mental deficiency are anomalies of development and malformations. The number of patients with known cerebral damage caused by prenatal infections is not large enough to deter

[1] P 0.01 for differences between groups 1 1b–g and 2a as compared with groups 4 and 5, both for height and skeletal age (Wilcoxon test).

TABLE 2 *Height age/chronological age ×100 according to diagnosis*

For diagnoses number see T ble 1

Height quotient	Diagnosis group 1	1b–g	2	2b	4[a]	5
110	0	4	2	5	1	16
90–109	3	22	8	27	41	35
80–89	7	21	12	7	9	9
80	30	34	21	3	5	0
Total	40	81	45	42	78	60
Mean	71	83	80	97	100	101

[a] Excl six cases with lesions of the base of the brain.

TABLE. 3 *Skeletal age/chronological age × 100 according to diagnosis*

For diagnosis numbers see T ble 1.

Skeletal age quotient	Diagnosis group 1	1 b – g	a +	2 b	4*	5
≥ 110	4	4	1	8	16	6
90–109	1	37	16	20	49	35
60– 89	16	27	14	8	15	7
< 60	4	9	14	2	1	7
Total	45	77	45	38	61	55
Mean	91	91	84	97	99	95

Excl. six cases with lesions of the basis of the brain.

mine their growth separately: some of them are dwarfed however

Cerebral damage in the perinatal period with gross neurological residual defects also cause growth retardation very often however skeletal age is as much below normal as height age In these patients with cerebral pal y of perinatal origin including kernicterus, the reduction in mean height–age is caused partly (for about one-third) by underdevelopment or atrophy of the lower extremities (ratio upper/lower segment too large) Taking this into account the slight difference in mean height age and skeletal age (Tables 2 and 3) would disappear altogether

Flexion contractures and scoliosis could be excluded as the cause of the retarded mean growth of these children, the same is true for the nutritional state determined by weight

In the other children with cerebral damage of perinatal origin but without palsy growth is virtually normal. This suggests that lesions in the perinatal period causing cerebral pal y also have a distinct influence upon growth and skeletal maturation. The higher frequency of prematurity in the perinatal cerebral palsy group does not explain the difference in growth of these children as compared with the perinatal group without palsy

In virtually all of our patients with cerebral damage of postnatal origin, i.e after the second month of life growth is normal whatever the cause of the dementia and whatever other accompanying neurological sequelae Many of these children suffer from cerebral palsy but are growing normally as opposed to the cases with cerebral palsy of perinatal origin. It seems that rather soon after birth the vulnerability of those parts of the brain which affect growth in perinatally cerebral palsied children has become much less.

In the six patients with direct lesions of the hypothalamic region (tuberculous meningitis) growth is much retarded, these children have been excluded from the tables and figures.

The normal growth in the so-called group of mild oligophrenia is according to expectation Many of these children have suffered most from adverse social hygienic and nutritional circumstances in their first years of life These factors which are often considered as a cause of growth disturbance in mental deficiency can be excluded as the explanation of dwarfism in our other patients.

The effect of sex and age is not given in the tables. Sex did not influence our figures both girls and boys show the above mentioned typical growth differences between the diagnostic groups. The differences in the age composition of the groups are rather limited in addition, age appears to have little effect only in cases of mongolism and prenatal injury there

is some reduction of the mean growth retardation in puberty and this does not affect the differences between groups. Differences in sexual maturation do not influence the general picture although in individual cases delayed or precocious puberty can of course temporarily either simulate or mask delayed height age and skeletal age.

Discussion

Our pre-formed diagnostic classification of mentally deficient children is considered satisfactory. Though this classification of course cannot be considered as the final word in the difficult problem of diagnosis in mental deficiency distinct differences in growth have been demonstrated with it. We hope that our diagnostic system may be useful in studying other biological and biochemical aspects of mental deficiency.

It is probable that the two general patterns of growth retardation found in mental deficiency may have two different causes. In the prenatal group the frequent combination of dwarfism with near normal skeletal maturation resembles an isolated growth hormone deficit or lack of response to this hormone as has been postulated also in another prenatal form of dwarfism i.e. Turner's syndrome [5]. Genetic dwarfism and primordial dwarfism as an inborn growth disturbance are other rather vague names for this kind of dwarfism. It is as yet impossible to distinguish between all these different groups.

The cerebral palsy group of perinatal origin, show a combination of dwarfism with retarded skeletal maturation suggesting trophic disturbances from cerebral origin. The same kind of dwarfism is found in dwarfism caused by other trophic disturbances as, for example malnutrition, chronic renal, cardiac or liver disease.

It should be mentioned here that signs of panhypopituitarism were found only in very few patients, whereas cases with hypothyroidism were excluded from our study: in all dubious cases serum PBI was determined. We have found two cases of gonadal dysgenesis (one case of Turner's syndrome in a girl and one case of Klinefelter's syndrome in a boy).

The differences in growth between the groups may also be useful in diagnosis especially in differentiating between cerebral palsy of perinatal and postnatal origin and between familiar imbecillitas and mild oligophrenia.

Summary

Using a diagnostic classification of mental defectives which is primarily oriented towards the time at which the cerebral lesions occurred, growth and skeletal maturation were investigated in 384 cases of oligophrenia aged from 3 through 16 years. Striking differences in growth were established which could not be explained by environmental influences, were the same in both sexes, and depended little or not at all on the age of the child. The disturbance of growth must indeed be related to the cerebral abnormality. In oligophrenia of prenatal origin dwarfism is very frequent and usually takes the form of retarded height with much less or no retardation of skeletal maturation. In cerebral palsy of perinatal origin the growth disturbance affect [illegible]bout equally height [illegible]nd sk[illegible]l tal maturation. Our [illegible]lassif[illegible]cation pr[illegible]ved t[illegible] be a [illegible]sef[illegible]l tool in studying gr[illegible]wt[illegible]. In some cases growth can be used in [illegible]iagnosis among mental [illegible]efectives.

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Department of Pediatrics
University Hospital
Leiden
The Netherland

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From the Pediatric Clinic, Karolinska Sjukhuset and the Department of Clinical Biochemistry Royal Veterinary College Stockholm Sweden

Calcium, Chloride, Cholesterol, Inorganic Phosphorus and Total Protein in Blood Plasma during the Early Neonatal Period Studied with Ultramicrochemical Methods

by BERTIL THALME

The ultramicrotechnique according to Sanz [15] was used in a previous investigation [19] and found to be very useful in pediatric clinical chemistry. Reasonable accuracy could be achieved with very small amounts of blood. It was therefore decided to use the ultramicrotechnique for the determination of some blood constituents in the early neonatal period. This report presents data for calcium, chloride cholesterol, inorganic phosphorus and total protein in blood plasma during the early neonatal period studied with ultramicrochemical methods.

Material and Methods

Healthy full-term breast-fed newborn infants from the maternity ward of Karolinska Sjukhuset were examined.

The newborn infants were examined in two ways. In a longitudinal study [illegible] newborn infants were investigated with serial examination within the first half hour of life, after 4 hours, 1 day, 2 days and 4 days.

Single examinations were done on 77–141 newborn infants at various times after birth up to 12 days of age. Total protein and cholesterol were determined on the same sample while calcium, chloride and inorganic phosphorus were determined on another sample. The newborn infants were grouped in age periods as follows: 0–6 hours after birth, 6–12 hours, 12–24 hours, 1–2 days, 2–3 days, 3–4 days, 4–6 days and 6–12 days.

Blood samples were obtained by pricking the heel as described by Pincus, Gittleman, Saito & Sobel [12]. The blood was collected in plastic test tubes. For comparison blood was also taken from students and members of the laboratory staff. In adults, however, the blood was taken by pricking one of the fingers. Blood samples with [illegible] of hemolysis were discarded. All determinations were made in [illegible] from the same blood sample. Methods and [illegible] ultramicro adaptation [illegible] method [illegible] presented [illegible] the following table with [illegible]

Table [illegible]

Analyses	Ultramicro adaptation of the method of	[illegible]	[illegible]	[illegible]	[illegible]
Calcium	Dahl & Klungsöyr [illegible]	[illegible]	[illegible]	11	[illegible]
Chloride	[illegible] 14	[illegible]	[illegible]	[illegible]	[illegible]
Cholesterol	[illegible]	[illegible]		[illegible]	[illegible]
Inorganic phosphorus	[illegible]	[illegible]	[illegible]	11	[illegible]
Total protein	[illegible] 27	[illegible]	[illegible]		[illegible]

TABLE 1

Analysi	Error in method	Error in method xpressed in % of mean value
Calcium, mg/100 ml	0.146	1.5
Chloride mEq/liter	1.54	1.4
Cholesterol, mg/100 ml	10.6	8.1
Inorganic phosphorus, mg/100 ml	0.136	1.9
T tal protein, g/100 ml	0.120	1.9

bers of subjects indicated and amounts required

Some modifications were employed which included use of concentrated sulfuric acid nstead of 50% sulfuric acid for cholesterol determination as recommended by Caraway & Fanger [ ] and use of Weichselbaum reagent [1] instead of that of Gornall, Bardawill & David [8] for determination of total protein These modifications gave more reproducible result and one pipetting could be omitted with the modified total protein method

The error in the method wa estimated in duplicat from the same blood sample obtained from each of the newborn infants 1–4 days of age in the single examination study The error in the methods is presented in Table 1

Further details concerning the ultramicromethods used, their ccuracy and modifications employed will be presented in another paper

The st tistical calculations were made according to current rules.[1] Calculations based on the 90 % limit for a 90% confidence has been carried out The following conditions for significance of lifferences:

	labeled
$p > 0.05$	no significance
$0.05 > p > 0.01$	probably significant
$0.01 > p > 0.001$	significant
$0.001 > p$	highly significant

where p is the probability that the differences are random results.

Results

In the longitudinal study the results for calcium chloride cholesterol inorganic phosphorus and total protein respectively are given in Figs. 1–5

The result of the single determination of calcium chloride cholesterol inorganic phosphorus and total protein are given in Figs 6–10 and Table 2.

Calcium (Figs 1 and 6)

The calcium level decreased rapidly during the first day of life after which it increased slowly during the following days.

The differences between the mean concentration at 0–6 hours and at 6–1 hours of age and between 0–1 hours and 1 hours were not statistically significant

After 12 hours of age the differences between the mean concentration were however significant

The newborn infants had a mean value slightly above that for adults.

Concomitantly with the decrease of calcium there was an increase in inorganic phosphorus.

[1] The statistical treatment of he results ha been carried out by Dr Staffan Ekblom of the Statistical Research Group of the University of Stockholm.

TABLE —

Age of newborns

Analysis	0–6 hr	6–12 hr	12 24 hr	1 2 days	2–3 days	3–4 days	4–6 days	6–12 days	Adults
Calcium, mg/100 ml									
	11	9	9	11	13	10	13	9	4
M	9.93	9.57	9.39	9 33	9.56	9.54	9.86	9 90	9.50
	0.737	0.304	0.649	0.300	0.493	0.331	0.438	0.437	0.225
$M \pm k$	11 7–8.1	10.4–8.8	11.0–7.8	10.1 8.6	10.7 8.4	10.4–8.7	10 9–8.8	11.0–8 8	10.0–9.0
Chloride, mEq/liter									
n	14	13	15	20	21	15	4	14	24
M	109.9	112.5	110.8	113.1	112.8	114.6	114.3	113.6	107.5
	3.06	2.15	3.03	3.29	3.79	2.64	2.44	2.83	2.81
$M \pm k$	117.0–101.9	117 6–107.3	117 7 103.9	117.8–108.0	121 0–105.7	120.6–108.6	119.3–109.3	120.1 107 0	113.4–101 7
Cholesterol, mg/100 ml									
	8	8	13	11	9	8	10	11	10
M	85.0	94.0	103.8	110.3	130.8	130 0	131.8	136.5	19[illegible]
	18 93	14 44	19.76	20.05	30.86	37.54	36.97	22.83	47 10
$M \pm k$	124.1 33.9	133.6–54 4	150.3–55.3	150.7–47 6	241.5–32.1	1_0–30.0	223.5–41 1	192.8–80.3	335.5–90.7
Inorganic phosphorus, mg/100 ml									
n	11	10	16	17	15	13	23	13	21
M	6.37	6.49	6.63	7.24	7 43	8.06	6.72	6.88	3.41
	0.680	0.733	0.973	0.401	0.901	0.658	0.780	1 054	0.327
$M \pm k$	8.00–4.75	8.35–4.63	8.88–4.51	8.33–6.15	9.20–5 61	8.54–6.38	8 37–5.07	0.30–4.33	4.00–..73
Total protein, g/100 ml									
n	8	8	10	19	13	9	14	11	24
M	6.55	6.73	6.83	6.86	6.86	6.84	6.70	6.30	7 01
	0.378	0.341	0.583	0.613	0.516	0.464	0.316	0.577	0.365
$M \pm k$	7.50–5 61	7 68–5.79	8.30–5.34	8 19 5 53	8 10–5.63	8 06–5.63	7 43–6.07	7.81–4.97	7 77–6.25

number of investigated newborns; M mean value; standard deviation; k = const t from Table A 16 in *Introduction to Statistical Analysis* by Dixon & Massey [8].
$M \pm k$ — the 90 % limits for 90 % on confidence.

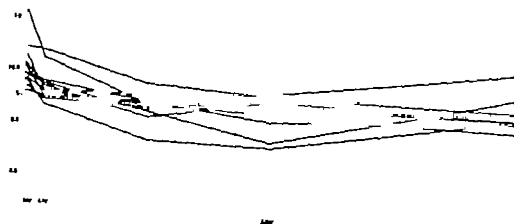


Fig. 1 Calcium in 11 hildren at various times after birth.



Fig -- Plasma hloride in 11 children t various times after birth.

)Chloride (Fig ° and ˜)

The mean values for all the groups in the early newborn period were similar

The concentration of chloride in adults wa lower than that during the first days of life

Cholesterol (Fig 3 and 8)

The level of cholesterol was low at birth and increased rapidly and steadily during the first three day of life The following days it remained fa rly constant This rise in cholesterol concentration was highly significant

The value in adults was markedly higher than the means for newborn infants three to twelve days of age

Inorganic phosphorus (Figs 4 and 9)

Th phosphorus level increased rapidly during the first three days of lif after which it lecreased during the following three lay

The lifferences between the mean con centration during these first three days were statistically ignificant Th lecrease in phosphorus value during the folk in days were not statistically significant

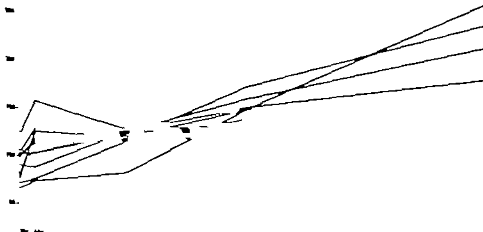


Fig. 3. Plasma cholesterol in 10 children at various times after birth.

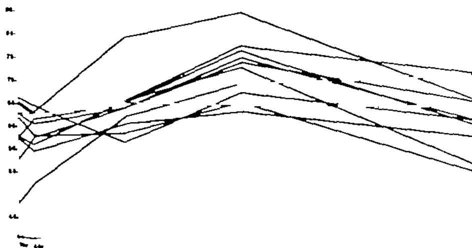


Fig. 4. Plasma phosphorus in 11 children at various times after birth.

Phosphorus
mg/100 ml

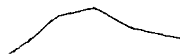


Fig 9 Plasma phosphorus from 116 newborns t various times after birth. The mean value is given together with the 90 limit for 90 confidence

Protein
g /100ml

Fig 10. Plasma total protein from 91 newborns t various times after birth. The mean value is given together with the 90 limits for a 90 confidence

TABLE 3. *The differences and their significance between the mean values for the examined age groups*

Analysis	Age of newborns							
	0–6 hr	6–12 hr	12–24 hr	1–2 days	2–3 days	3–4 days	4–6 days	6–12 days
Calcium, mg/100 ml								
Difference	0.36	0.29	0.04	0.23	0.02	0.32	0.04	
Significance	—	—	*** (0.04–0.04)					
Inorganic phosphorus, mg/100 ml								
Difference	0.12	0.20	0.65	0.19	0.47	0.24	0.14	
Significance	** (0.12–0.19) regression line: $y = 0.36 + 0.0195x$ (= 69; x = age in hours)				—	—	—	
Cholesterol, mg/100 ml								
Difference	9.0	8.8	16.4	17.6	2.2	4.2	1.7	
Significance	*** (9.0–17.6)				—	—	—	

[a] Regression line: $y = 8.17 + 0.133x$ (= 55; x = age in days).
[b] Regression line: $y = 85.4 + 0.666x$ (= 45; x = age in hours).

The differences and their significance between the mean values for the examined age groups is shown in Table 3.

Discussion

During this investigation as well as during earlier observations by Thalme & Åberg [19] it became evident that the ultramicrotechnique of Sanz [15] using the Beckman/Spinco Ultramicro Analytical System was valuable in pediatric clinical chemistry. The small volumes of blood necessary for the determinations could easily be obtained by using capillary blood. It was thus never necessary to obtain venous blood.

There is considerable variation in normal values as reported in the literature on blood constituents in newborn infants. The differences are partly the result of different methods of analysis used and partly also due to the technique of blood sampling.

In Table 4 values are shown as reported in the literature for calcium, chloride, cholesterol, inorganic phosphorus and total protein of blood plasma or serum of newborn infants.

The present values for cholesterol are in very good agreement with those reported by György [10], Rav & Phatak [14] and Rafstedt [13]; a marked increase in total cholesterol content of plasma was observed during the first 3–4 days of life. After that time the values were fairly constant during the following weeks. Josephson & Gyllenswärd [11] on the other hand found a higher cholesterol value in newborn infants but the cholesterol level in adults showed good agreement with the results of the present investigation.

As for total protein previous investigators found a rather varying "normal value" in newborn infants with a general tendency to increase with age. The values for total protein in the present investigation are in agreement with the results of other investigators [6, 9, 14]. Darrow & Cary [3]

TABLE 4

Analysis		Authors	Age in days	*	Mean	Range	Source	Method
Calcium	mg/100 ml	T[illegible] W R, Channel F G & Wood M T 1939 [20]	at birth	63	10.09	7.7 11.0	cord blood	Clark-Collip
			1 3	63	0.33	7.7 11.1	fontanel blood	Clark-Collip
			4–7	63	0.06	7.5 11.7	fontanel blood	Clark-Collip
	ml [illegible]	Sp[illegible]k, M L 1946 [18]	5	31	2.7	2.1 4.0	capillary blood	Clark-Collip
	mg 100 ml	R[illegible] H H & Plat[illegible]k, N M 1950 [14]	3 22	32	11.1	9.3 1[illegible]	fontanel blood	K[illegible] Tisdall
Inorganic phosphorus	g/100 ml	Todd W R, Ch[illegible] F G & Wood M T 1939 [20]	at birth	63	5.51	[illegible] 8.0	[illegible] blood	Fiske-Subbarow
			1 3	63	6.20	4.1 8.0	fontanel blood	Fiske-Subbarow
			4 7	63	5.74	4.0–7.1	fontanel blood	Fiske-Subbarow
		Bullock, J K 1930 [1]	1 9	13	4.8	—	—	—
	ml [illegible]	Sp[illegible]k M L 1946 [18]	5	32	4.2	3.0 7.1	[illegible] blood	Fiske-Subbarow
	mg 100 ml	R[illegible]y H H [illegible] Ph[illegible]k, N M 1950 [14]	3 [illegible]	79	5.1	4.5 [illegible]	f[illegible] blood	Gunther Greenberg
Cholesterol	mg/100 ml	Gyorgy P 1926 [10]	at birth	11	79	54–1[illegible]	cord blood	Bloor
		Sperry W M 1936 [17]	at birth	0	61	40 [illegible]	cord blood	Schoenheimer Sperry
			1	11	87	01 113	venous blood	Schoenheimer-Sperry
			3	6	107	83 1 3	venous blood	Schoenheimer-Sperry
			4 [illegible]5	63	113	71 109	venous blood	Schoenheimer-Sperry
		Rafstedt S 19 5 [13]	at birth	13	71	48 09	cord blood	Schoenheimer-Sperry
			3–10	13	111	110–107	capillary blood	Schoenheimer-Sperry
		Josephson B & G[illegible]mark C 1937 [11]	0 6	79	101	01– 40	capillary blood	Pearson-Stern McGavack
		Ra[illegible] H H & Plat[illegible]k, N M 1950 [14]	5 22	17	118	113–130	fontanel blood	Bloor
Chloride	ml [illegible]	Lorenz, J B, Gittleman I F Saito, M & Nobel, A B 1946 [1]	1	1	10	[illegible] 113	capillary blood	Schales-Schales
		G[illegible]mark C & Josephson B 1937 [9]	0 6	03	104	1[illegible]–107	capillary blood	Schales Schales
		Sp[illegible]k M L 1946 [18]	3	31	106	01 118	capillary blood	Schales Schales
	mg/100 ml NaCl	R[illegible]y H H & Plat[illegible]k, N M 1950 [14]	3 [illegible]	1	600	500 637	fontanel blood	[illegible]an Slyke
Total Protein	g 100 ml	Hickmans, L M, Finch E & Tooks, F 1943 [6]	0–14	19	6	4 7	capillary blood	Kjeldahl
		D[illegible] D C & C[illegible] M K 1933 [3]	3 11	20	5.5		venous blood	Kjeldahl
		Josephson B & G[illegible]mark C 1937 [11]	1 6	02	7.16	[illegible]–9.09	capillary blood	Josephson Anderson
		Ra[illegible] H H & Plat[illegible]k, N M 1950 [14]	3 [illegible]	40	0	6 3–7 8	fontanel blood	How

* Number of investigated infants.

reported a very low total protein valu using the Kjeldahl method. The result of Špirek [18] has not been included in Table 4 as his results are given for albumin and globulin separately

The values for chloride determination in newborn infants in the current study (113 mEq/liter) are somewhat high in comparison with those reported by Ray & Phatak [14], Pincus, Gittleman Saito & Sobel [12], Gyllenswärd & Josephson [9] and Špirek [18]. The concentration of chloride reported during the first days of life was higher than that in adults as al so pointed out by Gyllenswärd & Joseph son [9].

Todd, Chunard & Wood [20] 1939 sum marized the available literature dealing with blood calcium and phosphorus of newborn infants. Calcium had been deter mined by twenty authors in totally 83 cases and inorganic phosphorus had been determined in totally 64 cases by eight authors. The reported values in this study for calcium and inorganic phosphorus are in good agreement with those reported by Todd, Chuinard & Wood [20]. A lower phosphorus value was found by Bullock [1]. Špirek [18], using another technique found a lower calcium and a higher phos-phorus value in a day old infants. In –22 days old infants Ray & Phatak [14] re-ported a higher calcium and a lower phos-phorus value.

Todd, Chunard & Wood [20] mad an extensive study of calcium and phosphorus concentration in the serum of normal new born infants. A seasonal variation was re ported in 630 infants showing a higher value of serum calcium in autumn and winter and a slight increase in phosphorus in spring. They also compared the values for calcium and inorganic phosphorus in cord blood and fontanel blood in 65 new born infants. The results obtained are listed in Table 4. The authors pointed out that a the level of serum calcium of the 4 to 7-day-old infants increased over that of the 1–3 day old infant the inorganic phosphoru decreased so that the calci m phosphoru product remained virtually constant

Summary

Normal values for cal ium chloride cholesterol inorganic ph sphoru and t tal protein in blood pla ma from newborn infants and adults re given with th ultramicrotechnique acc rding to Sanz using the Beckman Spinc [illegible] Analytical System Some tat st call [illegible] nificant hanges with age were observed During the first three day [illegible] an in crease of h lesterol nd inorganic phos-phoru wa noticed nd concomitantl with the increase of inorganic phosphorus there wa a decrease of calci m On the ther hand n [illegible] h hanges were observed for th [illegible] blood nd t tal protein

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Pediatric Clinic
Karolinska Sjukhuset
Stockholm 60
Sweden

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From the Department of Pediatrics, University of Gothenburg and the Municipal Virological Laboratory Gothenburg, Sweden

Poliomyelitis in a Newborn Due to Intrauterine Infection

by ERIK LYCKE and LARS R. NILSSON

Case Report

The 36-year-old mother had previously four healthy children and one legal abortion. During this last pregnancy some edema of the feet and a slight anemia was observed, but otherwise she was healthy No fever or other signs of acut infectious disease had appeared before or after partus. During the course of the pregnancy she had been ex amined by physician at a maternity welfare center

The baby a girl, weighing 3550 g and 50 cm long was delivered spontaneously Oct. 14, 1961 at full term, in a right mento-anterior face presentation. The amniotic fluid was green-coloured but thin. The placenta, weighing 610 g, was deeply furrowed and had large coagulum t the margin.

On examination two and a half hours after delivery no abnormal findings were registered. A few hours later however paresis of the left arm was evident At two days of age the baby was extensively paretic with no spontaneous movements. The head f ll limply back when the body was raised. Patellar reflexes could be lutted bilaterally N respiratory difficulty was observed the sucking reflex was good and she swallowed normall There was moderat jaundice

During the next few days the function of the legs improved con siderably and the in fant could also move the f ngers of the right hand. At three weeks of age the baby had severe respiratory distress A pulmonary X ray showed a dens ty in the right upper lobe hich may have been an aspiration atelec t sis or a bronchopneumonia with atelectasis. The throat reflexes were by this time depressed and the thoracal breathing seemed to be little weakened. Treatment with antibiot ics was instituted, and the signs of respira tory infection disappeared in week.

On examination at 8 weeks of age the infant had normal breathing and normal swallowing function. She moved her legs normally and could turn her head. The shoulder girdle muscles were atrophic bilat erally The left arm was still totally paretic with trophic muscles In the right arm the muscular mass and tone were normal, except from the shoulder girdle but because of weakness in the latter movement we ery limited The mental development was judged as normal.

Laboratory Findings

Cerebrospinal fluid Oct 14: Color pale yellow cells: 63 leucocytes mm^3 (polynuclear 29 %, monon 71 %) no erythrocytes Protein 129 mg Oct 20 Colorless 34 leucocytes (pol n 2 monon 32) 2.6 rythrocytes/mm^3 Protein 143 mg Electrophor esis of liquor protei normal finding Oct 30 Colorless, 13 leucocy es 4000 fresh erythrocytes mm

Electromyography Oct 18 *Musc tibial s anterior si* no definit patholog l ... *Musc biceps brach et deltoideus dxt* lesion of the lower mot r neurone w l partially depen ed ... *(Dept ... the Neurophysiological Laborat ry ... of Gothenburg)*

TABLE I *Results of serological tests*

Blood specimens		Oct 16	Oct. 17	Oct 23	Oct. 31	Nov 13	Dec 8
Mother	CF	—	16	—	32	—	—
	NT	—	80	—	160	—	—
Child	CF	<4	—	<4	4	16	16
	NT	20	—	160	120	1*0	1*0

CF = complement-fixation test with polio type 1 antigen.
NT = neutralization test with polio type 1 virus in tissue cultures.
Titers are expressed as reciprocals of serum dilutions.

Electroencephalography Oct 19 A few episodes of abnormal activity with left-sided dominance (I Petersén)

Blood investigations Bilirubin in serum: Oct 16 15.8 mg%, Oct 18 17 4 mg%; Oct 19 10 4 mg %. The mother blood group O Rh the infant A Rh Immune anti bodies gainst the A factor could be de monstrated in the serum of the mother (L. Rytlinger the Blood Bank Laboratory Sahlgrenska Sjukhuset Gothenburg)

Virological Examination

Material and methods

Th mother Stool pecimens were col lected Oct 17 and Nov 1 .e 3 and 18 days after the del ery Blood pecimen were taken Oct 17 and Nov 1

Th infant Stool specimen were col lected at 3 and 1 day of age samples of urine on the 3rd day nd cerebrospinal fluid on the 3rd and 7th days of lif Blood specimens were taken Oct 10 Oct 23, Oct 31 Nov 13 Dec 8, when the child w 2, 9 1 30 nd 54 day old.

Stool, urine and cerebrosp nal fluid ere tested in cultures of H La nd trypsinized monkey kidney cells The cell cult res were kept in a medium consisting of H nks balanced salt solution cont ining 0.5 lact albumin hydrolysat calf serum, 100 I.U of penicillin and 100 gamma f strepto-mycin.

The serum specimens ere examined f complement f xation (CF) and neutraliza tion test (NT) The CF wa performed principally according to the method introduced by Fulton (4). The antigen s bstance used wa virus tissue culture fl id diluted 1:.. The antigen was standardized in box titra tions and four unit of antig n were employed in the serum titrations. Sheep blood suspen sions were standardized colorimetrically Hemolysine (rabbit serum) was used in amounts of four units. Patient sera ere diluted in fold steps beginning with 1 4 The diluent employed wa a veronal buffered saline (pH 7 6) cont ining Mg and Ca

NT was performed using 100 $TCID_{50}$ of virus and serum diluted in fold steps be ginning with 1 *0 and 1 20 The mi tures of virus and serum dilution ere allowed to react at room temperature f r one hour and then tested n t o cell cult res each. Neutralization wa considered to occur if the cythopathogenic effect f virus was neutralized n one of two test t bes used per dilution.

Result

A cythopathogenic agent typed a poliovirus type 1 wa isolated from the baby stool specimen collected at t o and three days of age but not from the stool specimen taken at 1 days of age No virus was obtained from the urine cere brospinal fluid or th nasal secretion From the mother type 1 ru wa re covered from the t ol pecimen collected

on the third day after delivery but not from the specimen of day 18.

The CF tests showed for the child a rise in titer against type 1 antigen from less than 1/4 to a titer of 1/16 in the last two specimens. The mother's first titer was 1/16 and the second 1/32. These differences were confirmed by repeated tests. The child's neutralizing antibodies rose from 1/30 in the first specimen to 1/160 in the second while a titer of 1/120 was registered for the following serum samples. The mother's neutralizing antibody titer also rose from 1/60 to 1/160.

The results of serological tests are summarized in Table 1.

Discussion

The paretic state of the infant led at first to a presumptive diagnosis of infantile spinal muscular atrophy (Werdnig–Hoffman's disease) which has been described in the new born [2]. It was apparent from the findings in the cerebrospinal fluid, however, that this diagnosis could not be correct. During the autumn of 1961 an outbreak of poliomyelitis due to type 1 virus occurred in Gothenburg with 50 cases of paralytic poliomyelitis. Poliomyelitis was therefore suspected although there was nothing in the history or clinical observations to indicate an infectious disease of the mother during pregnancy or at the time of the delivery. The virological examinations and the subsequent development of the disease in the child confirmed, however, the diagnosis *paralytic poliomyelitis*. The mother was not vaccinated against poliomyelitis. The child's paresis developed within a few hours after delivery. The disease must therefore have been caused by an intra-uterine infection with polio virus.

During pregnancy there is an increased susceptibility to poliomyelitis. In spite of this the incidence of polio virus infections causing disease in the fetus or in the new born child is small [1]. A number of cases reported, however, have been strongly suggestive of an intra-uterine infection with polio virus. Some of these cases have been insufficiently investigated, and suspicions arise as to whether many of the abortions reported as resulting from maternal poliomyelitis have actually been caused by intra-uterine polio virus infections. In other cases one cannot disregard the possibility that the virus was acquired first during the delivery and then by contamination by fecal material from the diseased mother. This has been pointed out by e.g. Kibrick [1].

There are some reports, however, in which intra-uterine infection is likely, and others where it is the only reasonable explanation of the abortion or the disease of the newborn child. In 1954 Schaeffer *et al.* [8] isolated poliovirus from placenta and fetus of a woman with a clinically typical paralytic poliomyelitis. Kibrick [1] has reported the isolation of polio virus type 1 from the central nervous system and the heart blood of the fetus of a woman with paralytic poliomyelitis. McCrae & Friedman [7] succeeded in isolating type 1 virus from a fragment of a necrotic fetus enclosed in intact membranes and decidua. The woman was in hospital for an aseptic meningitis and following the abortion she developed a paralytic poliomyelitis, also caused by a polio virus type 1 infection.

Intra-uterine infection with polio virus

may also occur during the last period of the pregnancy and manifest itself as a paralytic disease in the newborn child as in our case reported here Kreibich & Wolf [6] and Elliot & McAllister [3] have described two babies born with multiple flaxid paralyses The mothers were in hospital under the diagnosis of paralytic poliomyelitis. The children died one 12 hours the other 32 minutes, after the delivery and the histopathological examinations of the central nervous system agreed in both cases with polio virus infections. Shelokov & Habel [9] isolated type 1 virus from a mother and under conditions which opposed the possibility of a contamination at the delivery also from the child and the placenta. Another child reported by Jackson & Souw [5] was born with respiratory paralysis and died after 1½ hours. Polio virus type 1 was isolated from a stool specimen as well as from specimens of brain, spinal cord and heart tissue No virus wa recovered from the mother suffering from a paralytic disease Viremia with type 1 virus was demonstrable on the third day of life in a child which showed paralyses on the fifth day [10] No virus was recovered from the mother who developed a paralytic disease following delivery Finally Kibrick [1] has isolated type 1 from meconium of three healthy babies born to mothers with poliomyelitis The stool specimens were taken on the second and fourth days of life Quite a few other cases have been published. Available data are however incomplete so it is doubtful whether an intra-uterine infection might have occurred

Summary

Paresis appeared in a newborn on the first day of life The mother excreted polio-virus type 1 but had no signs of disease The virological examinations confirmed the diagnosis of poliomyelitis The early appearance of paresis is explicable only by the transmission of virus *in utero*

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(R. N.) Department of Pediatrics
Barnsjukhuset
(E. L.) Municipal Virological Laboratory
Göteborg
Sweden

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From the Department of Pediatrics, Karolinska Sjukhuset Stockholm

Tryptophan Metabolism in Infantile Spasm

by BO HELLSTRÖM and FRANCO VASSELLA

Abnormalities of tryptophan metabolism have been encountered in a great variety of conditions. In adult medicine the carcinoid syndrome with the symptoms related to increased production of 5-hydroxytryptamine and in psychiatry the psychotic states following the administration of 5-hydroxytryptamine antagonists are examples of conditions where a disturbed tryptophan metabolism is of significance. In the pediatric age group Hartnup's disease has been recognized as a metabolic disorder which also involves the breakdown of tryptophan (7).

A possible connection between disordered mental function in children and a disturbance in the 5-hydroxyindole pathways of tryptophan metabolism was indicated in the report by Sandler (12), who found a decreased production of 5-hydroxytryptamine in phenylketonuria whereas in other forms of mental defect such as those occurring in cerebral lipidoses and following maternal rubella an increased level of this metabolite was found. Increased levels of this metabolite were also found in six out of 23 cases of infantile autism and also in severely retarded as compared with mildly retarded children (13). O'Brien *et al.* (10) reported a diminished urinary excretion of a xanthurenic acid another tryptophan metabolite in mongoloid children following tryptophan loading.

Increased excretion of xanthurenic acid after tryptophan loading has been accepted as a sign of vitamin B_6 deficiency (11). A deficiency of this vitamin, with its function as a coenzyme in important steps of tryptophan metabolism, will modify the breakdown patterns and thus the amount of, for example, xanthurenic acid excreted will be increased. Nutritional deficiency of vitamin B_6 may cause convulsions in infancy (11). In vitamin B_6 dependency, a condition also associated with infantile seizures the requirement of the vitamin is very much increased. If this is not met with, convulsions may occur, but an ordinary daily supply of the vitamin prevents increased xanthurenic acid excretion (14). This may indicate that the altered tryptophan metabolism found in the deficiency states is not directly associated with the symptom of seizures. Several experimental and clinical data support the view that the glutamate group of amino acids and derivatives, some of them also requiring vitamin B_6 in their metabolism, is instead primarily involved (16). It has been postulated that vitamin B_6 dependency is an inborn error of meta-

bolism involving an enzyme system of the brain, the error resulting in an increased local requirement of vitamin B_6 in the central nervous system

The observations by Low *et al.* [9] with dietary experiments in cases of infantile spasms with hypsarhytmia and mental retardation raised the possibility that abnormalities of tryptophan metabolism could sometimes be found also in this heterogenous group of progressive infantile epilepsies. In one case the administration of a tryptophan-deficient diet caused a remarkable improvement in the incidence of seizures and in the EEG to be followed by a relapse when the treatment was discontinued

Jeune *et al* [8] found an increased excretion of xanthurenic acid after tryptophan loading in six out of seven infants with infantile spasm Only one child improved when given pyridoxine however and apparently the deficient enzyme function thought to be responsible for the impaired metabolism could not be restored in the other cases by giving the precursor to the coenzyme Cochrane [2] however who also found an abnormal tryptophan load test in five patients with the syndrome of infantile spasm and mental retardation, observed an improvement clinically and electroencephalographically after large doses of pyridoxine in his cases.

During the progress of the present study Bower [1] presented additional data on a disturbed tryptophan metabolism in cases of infantile spasm They were divided into a symptomatic group where most of the infants presented clear evidence of cerebral birth injury and a cryptogenic group where no etiological factor was known. Xanthurenic acid excretion after tryptophan loading revealed higher values in half of the cryptogenic cases, when compared with the excretion in the symptomatic group and in a control material. This latter group consisted of children admitted to the hospital for conditions unlikely to be associated with pyridoxine deficiency and of cases with convulsions (not infantile spasm) mental deficiency or both One of the latter however also had a high xanthurenic acid excretion and was apparently a case of pyridoxine deficiency Following treatment with ACTH and repeated tryptophan load tests xanthurenic acid excretion was lowered in all the ten cases of infantile spasm given this treatment irrespective of if they belonged to the symptomatic or the cryptogenic group or if they had normal pretreatment levels of xanthurenic acid or not. It was suggested that the effect of ACTH in several cases of infantile spasm could be mediated through increasing pyridoxine availability to the brain. A therapeutic trial with pyridoxine in three cases was followed by a temporary improvement in one case only This improvement did not include the psychomotor development. It was concluded that the metabolic error suggested by the abnormal tryptophan load tests was not a matter of simple pyridoxine deficiency

Present Investigation

The present investigation has been undertaken with the view of further exploring the possibility of abnormal tryptophan metabolism in etiologically obscure cases of infantile spasm. In the studies quoted above xanthurenic acid was the only metabolite investigated and, far

thermore, satisfactory control groups had been lacking In recent investigations the urinary excretory pattern of tryptophan metabolites along the tryptophan nicotinic acid pathway before and after tryptophan loading in larger groups of healthy infants have been studied [17 18].

Evidence of a tryptophan pyrrolase activity was present already at the end of gestation by the presence of metabolites in the urine of the newborn immediately after birth before clamping of the cord [17]. The changes in the excretory pattern with age were followed in fifty healthy infants one to twenty months old [18]. Metabolites along the kynurenine-nicotinic acid pathway excreted in the urine were studied qualitatively by two-dimensional paper chromatography In addition ... of this group were given a tryptophan loading test and the 24-hours urinary excretion of kynurenine, kynurenic acid, 3-hydroxykynurenine 3-hydroxyanthranilic acid and xanthurenic acid was estimated by quantitative paper chromatography

Material

As part of a cooperative study thirteen cases of infantile spasm from seven different pediatric department in Sweden were studied. The significant data from the case histories, from the clinical and laboratory findings are summarized in Table 1 where also the response to treatment with ACTH has been indicated.

All patients represent cases, where the etiology of the convulsive disorder was obscure or unknown. They all showed the typical pattern of infantile spasm with symmetrical myoclonic or tonic seizures of short duration, frequently resulting in a propulsive movement of the head and trunk and variable movements or postions of the extremities. These minor motor seizures as a rule occurred in a large number each day Other major attacks were present in four cases. Nine showed a moderat or severe degree of delay of psychomotor development In two cases this retardation was relatively slight with developmental quotient of 83 and 88 respectively In two cases the slow development had been obvious already from earliest infancy and before the onset of the spasms. The two cases, where no definit psychomotor retardation could be established were only 3½ and 6 months old at the time of the examination. The age of onset of the minor motor seizures varied from two weeks to 18 months. The EEG pattern of hypsarhytmia was present on one or several occasions in all cases; in three of them, however the highly abnormal irregular slow waves mixed with asynchronous and multifocal spikes and sharp waves occurred in a more discontinuous way especially when the infant was wake during the recording

As for possible etiological factors two infants had symptoms in the neonatal period that could suggest an intracranial birth injury A third one was a premature with a birth weight f 1460 g with uncomplicated postnatal course. In a fourth case the mother had a toxicosis during pregnancy and the infant developed a hyperbilirubinemia with a maximal level of indirect bilirubin of 27 mg ... not based on any known blood group incompatibility but not showing any sign of kernicterus or definite brain injury during the neonatal period. In a fifth case the spasms seemed t have a connection with smallpox vaccination, but a careful history revealed that slight symptoms had been present already before It cannot be excluded, however that a cerebral reaction t the vaccination hastened the development of brain lesion. In the eight remaining cases the cause of the disease was entirely unknown.

The duration of the symptoms before the metabolic studies were done varied from three weeks to 18 months. Five cases had received ACTH treatment prior to the studies, two of these received this treatment during the investigation. Altogether eleven

cases have been treated with ACTH with a conspicuous improvement of seizures and EEG-changes in three. In one of these the general psychomotor appearance of the infants also seemed to be improved. In eight cases the treatment had no favourable effect. Six infants were also given a short course with high doses of parenteral vitamin B_6 after the tryptophan load test without any clinical or EEG response.

Methods

Two consecutive 24-hours urine collections were made. On the second day an oral dose of 100 mg per kg body weight of L-tryptophan was given with the 10 a.m. feeding. Urine was collected in bottles under toluene. From both urine samples qualitative determinations were done and from the 24-hour sample after loading quantitative determinations of tryptophan metabolites were performed.

The qualitative analysis was accomplished by two-dimensional ascending chromatography on Whatman paper no 1 (22 × 28 cm) at a constant temperature of 26°C. Untreated urine 0.1 or 0.2 ml was applied to the paper by means of a micro-pipette of 10 microliters. Drying of the spots was hastened by cold air draught from a hair-dryer. Six different chromatograms were run for each urine sample, four with urine alone and two with urine to which known amounts of L-tryptophan, L-kynurenine, 3-hydroxykynurenine, anthranilic acid, 3 hydroxyanthranilic acid, kynurenic acid and xanthurenic acid were added. For the first run (overnight in the long dimension) a mixture of n-butanol: acetic acid: water (12: 3: 5 by vol.) [4] was used. After drying at room temperature the second run with distilled water as a solvent was performed. Identification of compounds was effected by studying their fluorescence in ultraviolet light and by characteristic colour reactions [4, 5, 6]. Quantitative determinations in duplicate were made from the urines after loading from the spots corresponding to L-kynurenine, 3-hydroxykynurenine, anthranilic acid, 3-hydroxyanthranilic acid, kynurenic acid and xanthurenic acid. They were visualized under ultraviolet light, marked, cut out, eluted and further analyzed according to the method of Coppini et al. [3]. When substances were present in very low amounts, two corresponding spots were eluted together in the same flask.

The tryptophan load test and the chromatographic analysis were repeated once in five cases and four times in one case.

The qualitative and quantitative findings were compared with the results from a control material consisting of fifty healthy infants whose ages covered the same range [18]. In twenty two of these quantitative data after tryptophan loading were available.

Results

Qualitative studies. The chromatograms of the unloaded urine samples from the cases of infantile spasm did not differ qualitatively from those of the healthy infants of corresponding ages and the most common excretory pictures of tryptophan metabolites as reported for this age group were also present in the pathological cases. *Quantitative studies.* The results of the quantitative determinations of metabolites along the kynurenine–nicotinic acid pathway excreted in the urine after tryptophan loading are given in Table. The figures are given in μM per kg body weight and 24 hours. From the control material mean values, the standard errors of the mean and the standard deviations of the amounts of the different metabolites excreted have been listed.

As can be seen from the table the amounts excreted in cases of infantile spasm after tryptophan loading were within normal limits (three times the standard deviation) concerning the metabolites kynurenine, 3-hydroxykynurenine, kynurenic acid, and 3-hydroxyanthranilic

TABLE 1 *Summary of clinical data of cases of infantile spasm*

Case	Sex	Age (months) at investigation	Age at onset of infantile spasms	Seizures other than infantile spasms	Hypsarhytmia	Mental retardation	Etiology	Response to ACTH
1	♂	6	4½ months	Grand mal	Present	Not diagnosed	Birth injury?	Improvement (seizures and EEG)
2	♂	17	2 months	—	Present	Present	Unknown	No improvement
3	♂	7	2 months	—	Modified	Present	Birth injury?	No improvement
4	♂	16	8 months	Grand mal	Modified	Present	Progression after small-pox vaccine	No improvement
5	♀	26	2 weeks	—	Present	Present	Unknown	No improvement
6	♂	6	5 months	—	Present	Present	Maternal toxicosis Neonatal hyperbilirubinemia	No improvement
7	♂	15	10 months	Grand mal	Present	Present	Unknown	No improvement
8	♂	7	2 months	—	Present	Present	Unknown	No improvement
9	♂	23	16 months	—	Present	Slight (IQ 88)	Premature (B.W 1460 g)	Not treated
10	♀	24	8 months	—	Modified	Present	Unknown	Improvement (seizures and EEG)
11	♂	13	6 months	—	Present	Slight (IQ 83)	Unknown	Improvement
12	♀	8½	5 months	Grand mal	Present	Present	Unknown	No improvement
13	♀	3½	2 months	—	Present	Not diagnosed	Unknown	Not treated

phate in the brain. Such processes form an important part of the oxidative metabolism of the brain, especially concerning the glutamate group with gamma-aminobutyric acid in an important strategic position In vitamin B_6 dependency states, probably representing a real inborn error of metabolism such an increased demand exists and if high doses of the vitamin are not given convulsions may occur True B_6 dependency states can, however not be a common cause of infantile spasm as the therapeutic response in most infants, including the six cases in the present material, in general has been poor

Although no definite conclusion can be drawn from the present investigation a possible hypothesis is that in cases of infantile spasm with the almost constant epileptogenic activity recordable from the brain the metabolic activity is increased with structural components fed into the oxidative metabolism These processes, irrespective of the primary cause, may imply an increased demand of pyridoxine in the brain with a consequent depletion of the vitamin from other enzyme system requiring pyridoxal-5-phosphate as a coenzyme e.g the tryptophan metabolism in the liver Giving pyridoxine in this situation may normalize the secondary disturbance of tryptophan metabolism but could not be expected to correct the abnormal metabolic activity of the brain.

The discussion above does not take into account the effect of ACTH on the xanthurenic acid excretion as demonstrated by Bower [1] nor does the hypothesis offer any explanation as to the therapeutic effect of ACTH and corticosteroids. The influence of these hormones on various metabolic activities and on intra- and extracellular ion gradients is extremely complicated and it seems probable that a study of tryptophan metabolism is a too narrow approach to elucidate this problem

Summary

Tryptophan metabolism along the kynurenine–nicotinic acid pathway was studied in 13 cases of infantile spasm by means of chromatographic analysis of metabolites excreted in the urine before and after tryptophan loading. Increased excretion of xanthurenic acid was found in several cases as compared with a control group of healthy infants. This finding is interpreted as a sign of relative vitamin B_6 deficiency in tissues concerned with tryptophan metabolism caused by an increased demand of the vitamin as a coenzyme in the pathological brain tissue. In most cases the disturbed tryptophan metabolism probably does not have any direct relation to the cerebral symptoms as these are not relieved by parenteral administration of high doses of vitamin B_6.

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Department of Pediatrics
Karolinska Sjukhuset
Stockholm 60
Sweden

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From the Department of Pediatrics, University of Umeå Medical School, Umeå, Sweden

Chronic Diarrhoea Caused by Monosaccharide Malabsorption

by BERTIL LINDQUIST and GUNNAR W MEEUWISSE

During recent years special attention has been focused on diarrhoea caused by an insufficient absorption of carbohydrates. Such an insufficiency may be part of a general malabsorption disorder e g celiac disease. Apart from this, there may be a selective defect of the absorption of different kinds of carbohydrates. In 1958 Durand [13] reported an infant who from birth presented chronic diarrhoea and lactosuria, presumably caused by a deficiency of lactase The next year Holzel, Schwarz & Sutcliffe [17] described two siblings with a defective lactose absorption. Since then diarrhoea caused by deficiency of other disaccharide-splitting enzymes has been reported Thus Weijers, van de Kamer Dicke & Ijsseling [24] have published three cases with defective absorption of sucrose, one of which in addition revealed a defective absorption of maltose. In 1961 Auricchio Prader Mürset & Witt [1] reported five cases of sucrose intolerance Of these there were two siblings in each of two families. Furthermore, the disorder could be traced back in each family indicating an enzyme deficiency with an autosomal dominant type of inheritance. A complete review of the reported cases of disaccharide intolerance has been published by Dahlqvist [9]

The diagnosis of disaccharide intolerance has mostly been based on abnormal results of the disaccharide tolerance tests (no rise of the blood glucose and/or a high disaccharide excretion with feces) whereas the tolerance test performed with the constituent monosaccharides has revealed a normal response Clinically the diarrhoea disappeared in all of these cases when the patients were fed a formula in which the carbohydrate consisted of glucose

Recently we have observed an infant who since birth presented watery stools due to an insufficient absorption of sugar In contrast to the cases hitherto published digestive studies performed on this infant revealed a defective absorption of certain monosaccharides.

Case Report

The patient was a girl, born Sept. 7 1961 She was the first child of second cousins. The birth weight was 3400 g and the length 49.5 cm. During her first three days of life no abnormality was noted On the fourth day the child developed a slight fever and began to pass frequent loose stools The child suckled normal amounts of breast-milk from her mother In spite of this there was a marked weight loss. She became severely dehydrated, but improved on parenteral fluid therapy A stool culture revealed

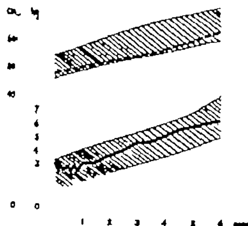


Fig 1 Weight (solid line) and length (broken line) of the patient. Dashed area indicates normal values ±2.0 D.

normal intestinal flora. In spite of the usual therapeutic measures the diarrhoea continued, and she produced 10–20 watery stools daily containing fine flocculent mucus. If fluids were given orally in sufficient amounts, her general condition remained unaffected and no further weight loss occurred.

On the suspicion of lactose intolerance the breast-milk was replaced by a special formula, containing carbohydrates as a mixture of dextrin maltose and sucrose t a content of 7.5%. N improvement was observed with this kind of feeding. On a similar formula, with a lower carbohydrat content (formula 1 see below) the stools became somewhat thicker and less frequent and she started to gain in weight; she was now about one month old (Fig. 1)

During the next months the same formula (formula 1) was given, except during periods of special digestive studies. The stools were still of semifluid consistency amounting t 300–500 g daily distributed ver 5–10 defecations. She howed a low resistance against infections, especially of the respiratory tract. When she developed an infection, her diarrhoea increased. Because of this, the different digest ve studies have been extended over a relatively long time. On the whole the weight gain and the increase in length have been satisfactory (Fig 1).

Routine examination at intervals did not reveal any abnormal physical signs.

Besides periodic treatment with sulfa drugs and antibiotics, the patient has continually been given vitamins, iron and, at regular intervals, gamma-globulins.

Laboratory f nd gs. The erythrocyte sedimentation rat as well as the whit cell and the differential cell count have been normal in periods free from infection. The hemoglobin concentration and the red cell count have shown subnormal values. The value for the serum protein has varied between 3.4 and .5 g% with normal electrophoretic distribution. The non-protein nitrogen le l was normal. Determination of the serum lipids showed normal values. Examination of the urine with "Clinistix has revealed a slight intermittent glucosuria. No prot inuria has been demonstrated. A 6-day fat balance study on a daily intake of about 40 g f t given as formula 1 (see below), showed a fat absorption f 93%.

X-ray of the intestinal tract showed normal conditions except a somewhat increased rate of passage f the contrast medium. X-ray of the lungs was normal.

Special Digestive Studies

Experimental diets. As the base diet d ri g the various digestive studies three special formulae were used, containing diff rent kinds f carbohydrates (T ble 1).

Sugar "balance studies. During pe i d 4–6 days, when the patient was fed ... formula, the beginning and the ... marked with carmine. The faeces ... titatively collected in 1 or 2-day ... The arrangement for the ... yielded a practically compl... the stools, including the fl id ... the different digest ... was continuously wat hed ... stools were immediat ly ... container and placed ... evitably some of the ... tained small amount ...

Each stool portion ... ration, analyzed ...

TABLE 1 *Composition of formulae supplied*

Diet	Cal/l	Protein %	Fat %	Carbohydrates (in %)				
				Starch	Lactose	Sucrose	Glucose	Fructose
Formula 1	660	3.1	4.0	1	—	3.7	0.8	—
Formula 2	640	3.0	4.0	1	3	—	—	—
Formula 3	640	3.0	4.0	—	—	—	—	4

glucose and fructose. The average daily fecal excretion of the different kinds of carbohydrate was then calculated.

Sugar-load test. Loading was performed with the following sugars: glucose, lactose, sucrose and fructose. At the beginning of each test the patient had been fasting for at least 5 hours, and about 4 hours after the test dose was given, the patient received her next meal. The kind of sugar under investigation was administered orally in a 10% water solution together with a special marker carmine or polyethylene glycol (PEG). The amount of sugar given was 2 g per kg body weight; the amount of disaccharide was calculated as the constituent monosaccharides after hydrolysis.

During 3 to 4 hours following the sugar administration blood samples were taken at intervals and analyzed for different kinds of sugar. Feces were collected for 1–2 days and each sample analyzed for sugar as mentioned above, for pH with a glass electrode apparatus and in some studies for PEG.

Intubation studies. Intubation studies of the intestinal digestion were performed according to the technique of Borgström, Lindquist & Lundh [7]. After the administration of a test meal, which besides normal food constituents, contained the water soluble but nonabsorbable substance PEG as a reference substance, samples of the intestinal contents were collected in fractions by siphonage for 3–4 hours. In one study when the end of the tube was located in the distal duodenum, the collected samples were analyzed for PEG and for amylase, trypsin and lipase; the test meal here consisted of 150 g of formula 1. In another study, when the distal end of the tube was located in the second loop of the jejunum, the collected samples were analyzed for glucose and fructose as well as PEG. The test meal—170 g in this study—consisted of formula 3, except that the carbohydrate portion was composed of equal parts of glucose and fructose. From the ratio of glucose and fructose to PEG in the test meal, and from the same ratios in the intestinal content it was possible to calculate the percentage absorption of the different sugars. The values thus obtained refer to a given sample collected during a certain time interval at the specified level of the intestine.

Analytical methods. Total reducing sugar in blood was determined according to the method of Somogyi [23] and Nelson [21]. Sugar in feces after deproteinization was estimated by the anthrone method [--]. Glucose was measured by the glucose oxidase method as described by Dahlqvist [10]. Fructose was estimated with β-indolyl acetic acid, a method described by Heyrowsky [16] for the determination of inulin. This method also measures fructose in unhydrolyzed sugars, e.g. as a component of sucrose. Sugar chromatographic studies were performed according to Bickel & Souchon [3] with some modifications; see also Bickel [2].

The polyethylene glycol (PEG) concentration was measured by a turbidimetric method after precipitation of the protein [18].

Tryptic activity was determined spectrophotometrically with a specific substrate (N benzoyl-arginine ethyl ester) according to Lundh [19]. The trypsin concentration is given in μg/ml. Amylase was determined by the method of Meyer, Noelting & Bernfeld [20]. The amylase activity is expressed in

TABLE _. *Results of the sugar balance studies*

Diet	Kind of sugar	Sugar intake (g/day)	Feces average wet wt. (g/day)	Fecal sugar[a] % of wet feces	Fecal sugar[a] Daily excretion (g)
Formula 1	sucrose, glucose	35	350	0.5(0._ 1)	2(1–6)[b]
Formula 2	lactose	30	400	1 4(1 2)	6(3–9)[c]
Formula 3	fructose	40	145	0.012(0.005–0.0_2)	0 02(0.005–0.045)

Mean and range
Mainly glucose and only small amounts of fructose
Approximately three parts of glucose to one part f galactose

units (1 unit = 1 mg f maltose liberated in 3 minutes by 1 ml f the sample at 25°C) Lipase was assayed with a spectrophotometric method, using triolein emulsion as substrate [4].

Results

Sugar "balance studies The results of these studies are presented in Table 2.

During the "balance" studies on formulae 1 and 2 the sugar ingredient in the former being sucrose and glucose and in the latter lactose the average daily amount of sugar in feces was 2 g and 6 g respectively The daily sugar intake was 35 g on formula 1 and 30 g on formula _ In a similar study on the fructose-con

Blood glucose mg%
150
100
50
0
0 1 2 3 hour
glucose

Fig. 2 A Blood glucose level fter an oral load of 2 g glucose per kg body weight

Fig B Concentration of sugar in wet feces fter an oral load of 2 g glucose per kg body weight. Before and fter he load the infan was fed formula 1 (see ext). O total sugar ● glucose Arbitrary scale The degree of colour was visually estimated

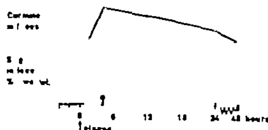


Fig. 3 Concentration of sugar in wet feces in normal subject of comparable age (3 months) at the time of the study presented in Fig. 2 after an oral load of 2 g glucose per kg body weight. O total sugar; ● glucose; 1 Arbitrary scale. The degree of colour was visually estimated.

taining formula 3 the average daily fructose excretion with feces was 0 02 g the daily fructose intake being 40 g

Sugar-loading test The results of these tests are presented in Figs. 2–6

When *glucose* was given, no appreciable rise of the blood glucose level was observed (Fig 2*A*) The fecal glucose content rose markedly within the first 4 hours it amounted to 2 % of the fecal wet weight, and during the following 24 hours there was then a gradual decrease to the preloading values (Fig 2*B*) A normal subject of corresponding age studied in the same way showed no significant rise of the glucose content in feces (Fig 3); in fact, the highest value found during this loading was 0 1 %.

Loading with *lactose* was not followed by a normal response of the blood glucose level (Fig 4*A*) There was a marked sugar loss with the feces during the 24 hours following the lactose administration, with maximal values between 6 and 10 hours This amounted to around 2 % of feces wet weight, half of which was glucose (Fig. 4*B*) Chromatographic studies revealed that

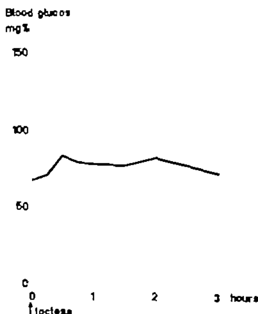


Fig 4*A* Blood glucose level after an oral load of 2 g lactose per kg body weight.

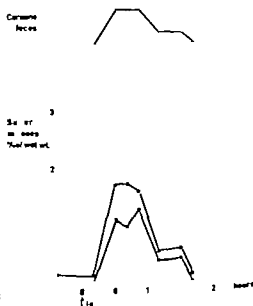
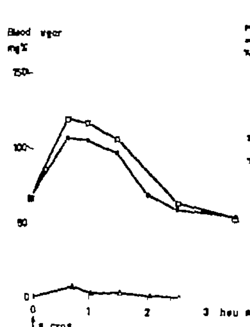
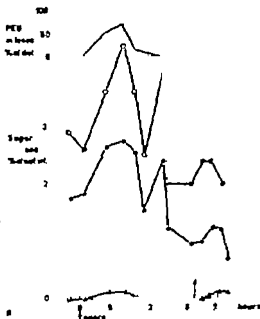


Fig. 4*B* Concentration of sugar in wet feces after an oral load of 2 g lactose per kg body weight. Before and after the load the infant was fed formula 1 O total sugar; ● glucose; 1 Arbitrary scale The degree of colour was visually estimated.


Fig 5A Levels of total sugar glucose and fructose in blood after an oral load of 1.8 g sucrose (see text) per kg body weight. □, total sugar; ● glucose; △ fructose.


Fig 5B Concentration of PEG and sugar in wet feces after an oral load of 1 9 g sucrose (see text) per kg body weight. Before and after the load the infant was fed the fructose-free formula —t 20 hours after the sucrose load this formula was replaced by formula 1 ○ total sugar; ● glucose; △ fructose.

the rest of the fecal sugar consisted of galactose; no lactose could be demonstrated.

The loading tests described above were performed with the patient fed formula 1 in which the sugar consisted of sucrose and glucose. The following two tests were carried out on a fructose- and sucrose-free diet (formula 2).

Within 1 hour after the *sucrose* load there was an increase of the blood-sugar level of about 50 mg %, determined as total reducing substance (Fig. 5A). The corresponding values for glucose and fructose were 40 and 10 mg %, respectively when measured by specific methods (see above) As invertase treatment of the blood filtrate did not accomplish an augmentation of the glucose reading the fructose in these samples must have been present in free form and not as sucrose On formula 2 there were relatively high pre-loading values of sugar in the feces. Nevertheless, a rise of the total sugar as well as of the glucose content could be observed after the loading with values from 6 to 4 4 and 1 9 to 2 8 % of the wet feces respectively (Fig 5B) In addition a slight fructose excretion in the feces could be demonstrated. Paper chromatography showed the fecal sugar to consist of glucose fructose and galactose; no disaccharide could be demonstrated.

Loading with *fructose* was followed by a marked rise of the blood sugar (Fig 6A) the increase being 110 mg % (total reduc-

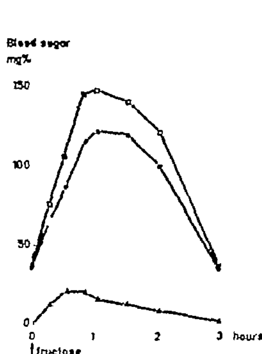


Fig 6 A Levels of total sugar glucose and fructose in blood after an oral load of 3 g fructose per kg body weight □ total sugar; ● glucose; △ fructose

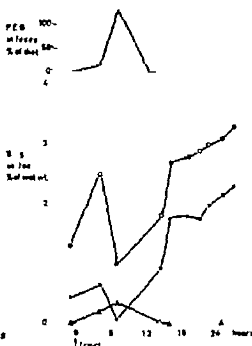


Fig. 6 B Concentration of PEG and sugar in wet feces after an oral load of 3 g fructose per kg body weight. Before and after the load the infant was fed the fructose-free formula 2 (see text). ○ total sugar ● glucose; △ fructose.

ing substance) The corresponding values for glucose and fructose were 80 and *0 mg %, respectively In the feces (Fig 6 B) a small fructose excretion was noted with a maximum value at about 6 hours after the loading Corresponding to this the glucose content fell to a very low valu. Even the value for the total sugar decreased at this interval, the preceding high value is presumably ascribable to the foregoing meal As seen from the same figure there was a later increase of the levels for total sugar as well as for glucose this is probably due to the carbohydrates in the meals following the loading test.

The peaks for the excretions of the different sugars in the feces after the loadings were well related to the maximum concentration of the marker given (carmine or PEG)

pH determinations on the stools in connection with the loading tests showed decreased values (the pH ranging from 4.0–6.5) which was in accordance with their sour smell.

Intubation studies The results of these studies are presented in Figs. 7 and 8.

From the PEG values it is seen that the test meal was diluted about twofold when passing through the duodenum and upper jejunum, this finding being in agreement with results obtained in normal subjects [7] The figures obtained for the concentration of trypsin in the distal duodenum (Fig 7) are also of the same order as those obtained by these authors [7] The amy

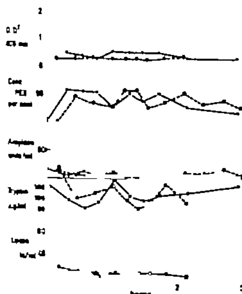


Fig. 7 Concentration of amylase trypsin and lipase in the intestinal content of distal duodenum after administration of test meal based on formula 1 The two symbols represent different values obtained from studies performed on two successive days. 1 Optical density measured at 400 mμ, representing admixture of bile [6].

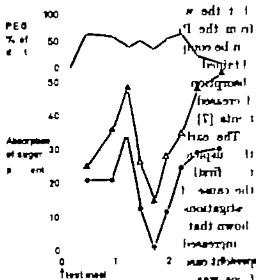


Fig 8. Absorption data for glucose and fructose at the level of the second jejunal loop when simultaneously fed in test meal based on formula 3. ● glucose △ fructose

lase concentration however was somewhat lower in this patient than found in a series of normal subjects [6] Concerning lipase normal data is scarce in this age group. The values obtained seem however to be reasonably normal.

It has been shown previously that the intestinal contents remain free from reducing sugars when carbohydrates are not fed [3] In the present case the absorption values for glucose obtained after intubation of the upper jejunum varied largely during the course of the study but on the whole the absorption was around 25 (Fig. 8) Furthermore the absorption values for glucose were constantly lower than those for fructose the difference in percentage absorption being about 10 except at the end of the study, when it increased

Discussion

The intubation studies in the case reported here revealed that the production of trypsin and lipase in response to a test meal was probably within normal limits As mentioned above the amylase concentration was somewhat decreased. However significant amount of enzyme activity could be demonstrated and this activity should reasonably suffice to digest the small amount of starch (1) in the diets supplied (formulas 1 and) In any event the abnormal stools cannot be due to insufficient digestion of food caused by deficiency of pancreatic enzymes. Signs of general malabsorption could not be demonstrated there was no steatorrhoea In this connection it may be mentioned

that the water absorption as evaluated from the PEG values was normal. This can be compared with the low PEG values obtained in patients with general mal absorption (celiac patients) indicating a decreased water absorption in these patients [7].

The early onset of the disease raised the suspicion of a disaccharide malabsorption firstly malabsorption of lactose as the cause of the diarrhoea. Results of investigations recently published [1] have shown that in this disorder one can expect an increased excretion of fecal sugar. In the present case the excretion of sugar with the feces was in fact increased. Such an increase could be demonstrated in the stools when the patient was fed a lactose-containing formula (Table 2) as well as after a loading test with lactose when the patient was fed a lactose-free diet. Concomitantly determination of the blood sugar after the lactose load revealed a flat curve. However studies on the fecal sugar composition showed *no lactose but only* the lactose-constituent *monosaccharides* glucose and galactose. The hydrolysis of lactose thus was not disturbed in this patient.

In patients suffering from lactase deficiency a normal response of the blood sugar is obtained on loading with the lactose-constituent monosaccharides. In the patient here reported there was, however no such response. The remarkable finding on loading with glucose was a flat blood-sugar curve and a high fecal excretion of glucose together indicating a poor absorption of glucose.

Auricchio *et al.* [1] have shown that in patients suffering from deficiency of the sucrose-splitting enzyme (invertase) after loading with sucrose there could be demonstrated a considerably increased fecal excretion of sucrose but not of glucose. The results from the sucrose-loading test in the present case indicated that the patient was able to split sucrose. Thus in this test *no sucrose but instead a large* amount of glucose and a smaller amount of fructose could be demonstrated in feces. Furthermore, in conditions of invertase deficiency the blood-sugar curve remains flat on a loading with sucrose [24]. In the case here reported, however a significant rise of the blood-sugar level was observed after loading with this disaccharide. This rise must apparently be attributed to fructose absorption. It is true that the increase of the fructose level in blood was small. It is known however that after intestinal absorption fructose is very rapidly transformed into glucose in the intermediate carbohydrate metabolism [16].

As could be expected from the foregoing studies a considerable increase of the blood-sugar level involving total sugar as well as glucose, was observed after fructose loading. Furthermore the fecal sugar decreased on this loading. These results were confirmed by a "balance" study with fructose: as seen in Table 2 only small amounts of fructose were recovered from the stools.

In line with the results obtained from the loading tests and the "balance" studies, the study of the absorptive capacity of the upper intestinal tract, performed by the intubation technique showed a preferential absorption of fructose to glucose when the two were given simultaneously. Even the glucose absorption per se was decreased at this level. Previous in-

vestigations with the same technique on infants of the same age group have shown that at this level glucose is absorbed to at least 50 % [7]. It may be added that according to present knowledge glucose is normally absorbed at a higher rate than fructose [12].

As known, half of the molecule of sucrose and lactose consists of glucose the other half being fructose and galactose respectively. When, in the present case loadings with these two disaccharides were compared, an important difference appeared. the fructose component was readily absorbed, whereas galactose was apparently handled similarly to glucose

Taken together the digestive studies have failed to show a deficiency of the disaccharide-splitting enzymes invertase and lactase Instead, in the present case the sugar absorption was found to be disturbed at the monosaccharide level, but only concerning glucose and galactose-fructose was well absorbed. Glucose and galactose are presumed to be actively absorbed, and by one and the same mechanism (see Crane [8]). Apparently this mechanism is not functioning in the present case. A selective malabsorption of certain monosaccharides does not seem to have been previously reported in the literature

The results from the digestive studies give good explanation of the clinical symptoms. The diarrhoea was most pronounced on breast milk, and also on a lactose-containing formula it was severe A sucrose containing formula caused a certain improvement, and finally on the fructose formula the diarrhoea subsided completely

According to Weijers *et al.* [*4], the diarrhoea in disaccharide malabsorption may be caused by bacterial fermentation of non-absorbed sugar with consequent irritation of the intestine by acid compounds and other metabolites. The high sugar content in feces demonstrated in this case and in patients with disaccharide malabsorption [1] offers another and more simple explanation for the watery stools; these may be due to an osmotic effect. In fact this mechanism was already postulated by Durand [14].

According to Borgström *et al* [5], the action of the disaccharide-splitting enzymes is confined to the intestinal cells and the disaccharides are claimed to be absorbed as such [11]. As mentioned above in the present case the non-absorbed portion of the orally fed disaccharides was recovered from the feces as the constituent monosaccharides This does not however necessarily set aside the theory presented by these authors the disaccharide components may after being split intracellularly diffuse back to the intestinal lumen, especially if it is presumed that the disaccharidase activity is exerted superficially in the intestinal epithelium.

The fact that in the present case glucose and galactose were absorbed at a *lower* rate than fructose is difficult to explain in view of present opinion on the mechanisms of monosaccharide absorption [5]. According to this fructose is *not* actively absorbed. If fructose were absorbed only by simple diffusion, one would expect, however that in this case glucose and galactose would be absorbed to the same extent as fructose The difference found in the absorption rate of glucose and fructose may be explained in several ways, e g (1) fructose diffuses faster than

glucose (2) fructose *is* actively absorbed, but by another mechanism than glucose, (3) glucose in the intestinal epithelium is trapped by the first step(s) of the active absorption mechanism, the failure being located in a later step. A local accumulation of glucose brought about in this way may then impede diffusion of glucose.

We propose to call the condition described above monosaccharide malabsorption. In this connection it may be mentioned that there are unfortunately two different groups of disturbed carbohydrate metabolism both given the termination "intolerance". First, conditions of disturbance in the intermediate carbohydrate metabolism e g fructose intolerance (15) second, the group of insufficient sugar absorption from the intestinal tract of which hitherto only the disaccharide intolerance has been described. In our opinion it would be better to reserve the term "intolerance" for the group of conditions first mentioned and to term the second group of conditions "sugar malabsorption".

It is apparent from the discussion presented above that the findings obtained to date actualize many questions on the mechanisms of sugar absorption. Further investigations including renal function studies aimed at a clarification of the disturbed monosaccharide metabolism in this patient, are in progress.

Summary

A form of intestinal malabsorption, not previously described causing chronic diarrhoea from birth is presented. The mechanism of this condition seems to be a selective disturbance of the absorption of the monosaccharides glucose and galactose. The clinical picture is almost the same as that found in conditions of deficiency of disaccharide-splitting enzymes; the difference is, however that the patient fails to improve on a diet based on glucose as the carbohydrate. In contrast, on a similar diet based on fructose the diarrhoea disappears. The implications of the different digestive findings obtained are discussed in relation to general mechanisms of sugar absorption.

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Department of Pediatrics
Centrallasarettet
Umeå
Sweden

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CASE REPORT

Post Mortem Diagnosis of a New Double-Trisomy Associated with Cardiovascular and Other Anomalies[1]

by KARL-HENRIK GUSTAVSON BJÖRN I IVEMARK, PER ZETTERQVIST and J A BÖÖK

From the Institut for Medical Genetics University of Uppsala and the Department of Pediatric Pathology Karolinska Sjukhuset Stockholm Sweden

In addition to trisomy 21 with its phenotypical manifestations (mongolism or Down s syndrome) two less common autosomal trisomic syndromes are now recognized as clinical and cytogenetical entities One of these conditions, involving chromosome no 17 or 18 [4 27] has also been observed in association with a triple X constellation [29], in a way analogous to the combination of mongolism and Klinefelter's syndrome [7 11 14 16 17] The other trisomy no (13–15) (D trisomy or Patau s syndrome) has been reported in a few children presenting a rather characteristic combination of malformations [20 22] We have observed an apparently identical trisomy which was also combined with an extra small acrocentric chromosome in cells cultivated from bone marrow taken at autopsy from a newborn boy

The gross post mortem findings included microphthalmia polydactyly ventricular septal defect intracranial venous anomalies and dysplasia of the kidneys liver and pancreas. The bone marrow cultures were initiated about 72 hours after the death of the patient.

History and Clinical Examination

The mother born in 1936, and the father born in 1935, were both healthy Mongolism, gross malformations, significant mental retardation, or other important diseases or defects were not known to have occurred among the relatives. The first pregnancy resulted, after seven months duration, in the birth of a boy His birth weight was 1150 g and he survived for only 8 hours. At autopsy performed by one of us (B.I.I.) the cause of death was found to be an intraventricular hemorrhage No malformations were recorded.

The second child, a boy who is the object of this investigation, was born 10 days after the average term. The delivery was normal. His birth weight was 460 g The orbits and the eyeballs were quite small. An area of ulceration, measuring 2 3 cm, was observed over the anterior fontanel. His ears were low set but of normal appearance H had small 6th digits on the ulnar side of both hands. There were no physical signs of congenital heart disease and his ECG was normal. The abdominal examination revealed supra-umbilical hernia, 1.5 cm in diameter Epicanthic eyefolds, oblique palpebral fissures brachycephaly increased skin fold of the

[1] Supported by grants from the Swedish Medical Research Council, the Swedish Atomic Research Council, the International Atomic Energy Agency the U.S. Atomic Energy Committee and the Foundations Fund for Research in Psychiatry to Prof J A. Böök and by grants from the Fund for Prenatal Research from the *Expressen* newspaper Stockholm, t Dr K. H. Gustavson and Dr B. I Ivemark.



Fig. 1. Heart. Right atrium and ventricle with hypertrophy of walls and dilatation. Arrow points to the papillary muscle of the conus, posterior to which the ventricular septal defect is seen. T the right of the arrow the crista supraventricularis is clearly seen.



Fig. 2. Heart from the left side. Arrow points to the defect, located below he right and anterior (non-coronary) cusps of the aortic orifice The cleft mitral is artifact. The apparent thickness of the left ventricular wall is due to tangential section through the septum.

back of the neck, clinodactyly or other signs characteristic of mongolism were bsent Signs of postmaturity such as meconium staining, dry and scaly skin or abnormally long finger nails were not observed. Apnoea occurred immediately after birth and lasted for about 8 minutes until respiration could be initiated with the aid of intubation. He had several attacks of cyanosis, and died about 24 hours later following generalized convulsive seizure

Pathology

Gross examination

Autopsy was performed about 40 hours after death. The body length was 45 cm and the weight 2285 g. The circumference of the head was 3* cm, of the chest and bdomen 25 cm and 23 cm respectively A supraum bilical hernia, measuring 1.5 1.5 cm, was covered by normal skin. Two boneless ac cessory fingers were present, both attached to the 5th fingers by a thin strand of skin. The tips of these extra fingers had dysplastic nails. An ulceration, measuring 2 3 cm, wa found over the anterior fontanel. The eyes were small, but neither epicanthus nor other external signs of mongolism were discovered. No hemangiomas were seen. The lips, nailbeds and skin were cyanotic

The *lungs* were smaller than the verage for his age, both together weighing 24 g (normal for 45 cm body length 46 ± 16 g [8]) The lobation was normal and the paren chyma was telectatic and slightly congested. The pulmonary arteries and veins displayed no gross abnormalities.

The *heart* was normally located and mode rately dilated. It transverse diameter was

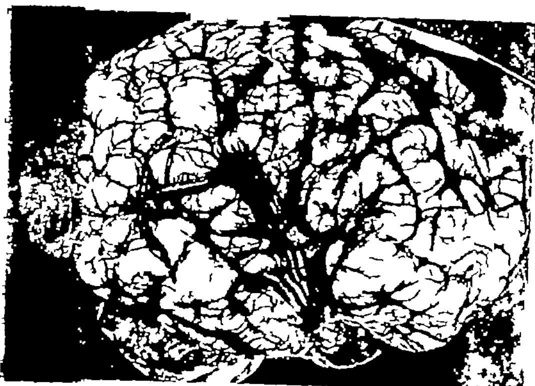


Fig. 3. Brain, showing excess of large veins in the temporo-parietal region.

the chest diameter in the same plane was 6.5 cm. The weight of the heart was slightly reduced (12 g; normal 15.1 ± 4.8 g) and dilatation was restricted to the right atrium and ventricle. The venous return and the great arteries were normal. No pathological changes were observed in the atrial septum and the foramen ovale. All ostia appeared normal. A defect was found in the posterior part of the ventricular septum behind the papillary muscle of the conus (Fig. ...). Its internal circumference was the same as that of the ductus arteriosus (i.e. 20 mm). The thickness of the wall of the right ventricle was 7 mm and that of the left 5 mm.

The *kidneys* were small and of equal size (weighing together 12 g; normal 21.6 ± 6.7 g). The renal pelves and urinary tract displayed no gross anomalies. The testes were located in the abdomen.

Otherwise the findings were essentially normal except for the fact that the liver adrenals, thymus and pancreas were approximately 40% underweight as compared with average findings. The spleen was normal and two umbilical arteries were present.

The examination of the *cranial content* revealed an increased venous vascularization of the leptomeninges on both sides (Fig. 3). Bilateral microphthalmia (bulb diameter 0.8 cm) was also present. No hemorrhages or areas of calcification were found in the brain. The ventricular system was normal as were also the choroid plexus and the brain arteries. No localized angiomas were found.

Microscopic examination

Cortical cysts, an excess of blood vessels and a medullary dysplasia were first discovered in the kidneys. This suggested a further search for vascular anomalies, and, in fact, an increased vascularity was found in the liver and pancreas as well as in the heart and lungs.

The *kidneys* displayed three apparently



Fig. 4. Kidney Normal cortex and dysplastic medulla, showing the small umber of collecting ducts, of which few re dilated. Arrows point to large veins in the pelvic tissue. 29



Fig 5. Kidney Marked dysplastic papilla with inverted pelvic end (below), few ducts and excess of vessels. Note dilated veins of cortico-medullary zone (arrow) 29.

different lesions, i.e. ( ) cortical cysts, (b) medullary dysplasia, and ( ) excess of blood vessels The cysts were irregularly distributed at all level of the cortex of both kidneys (Fig. 7). A high columna epithelium lined the wall, the basement membrane of w ich was partly thickened and hyalinized (Fig 8) The cysts contained protein-like material but no glomerular tufts were identified in routine preparations. The cortex showed no signs of infection, but few areas of cartilage were found beneath the capsule (Fig 6). Several pyramids showed paucity of col lecting ducts and were composed of primitive connective tissue which was bnormally rich in vessels On the whole the medulla was more vascularised and had a less well developed parenchyma than the cortex ("medullary dysplasia) [6] The excess of blood vessels was seen mainly in the pelvic tissue close t the calyces minores (Fig 4), in the medullary pyramid (Fig 5) and in the cortico medullary zone. The vessels were wide thin-walled and vein like The arteries ppeared normal.

In the liver the connecti e tissue of the portal tracts was hyperplastic (Fig 9) Such areas had a surplus of blood vessels and contained several nerves and large bile ducts which seemed hyperplastic. N cysts were seen here. A few hematopoietic foci were seen in the sinusoids.

A patchy hyperplasia of the connective tissue, the vessels and the duct was found in the pancreas (Fig 10) Signs of acti hematopoiesis were seen some parts



Fig 6. Kidney Area of cartilage subcapsular region. X to dilated tubule with thick basement membrane (arrow). 184.



Fig 7 Kidney Cortical cysts, some of which display thick basement membranes. 29

The *lungs* showed atelectasis and in the eft lower lobe signs of a recent pneumonia. e veins appeared enlarged and too nu merous, with extensions to the subpleural areas, but no true angiomas were present. There was no capillary congestion

Enlarged veins were seen extending in groups deeply into the *myocardium* The significance of these bservations is uncer tain.

The *brain* showed n bnormality other than the localized increase of large veins of the leptomeninges in the temporoparietal regions. There were no true angiomas, nor signs of calcifications of the vessel walls or cerebral cortex

The *eye bulbs* showed pronounced microphthalmia with fragmented and cataractous lenses, rudimentary irises and primitive ci llary bodies showing rosettes (Fig 11). The canals of Schlemm could not be demonstra ted unequivocally The optic nerves were reduced in size, and glial elements, but no neurofibrils or myelin could be identified.

As expected in a male, the *skin* showed no chromatin positive nuclei Histological examination of other tissues including the thymus, testes, thyroid, larynx, rib and spleen revealed no definite pathological changes.

Cytological observations

The cytological investigation was based on long-term cultures of bone-marrow obtained from three ribs about seventy-two hours after death.

The cells were cultured *in vitro* and processed according to the technique developed



Fig. 8. Kidney Higher magnification of previous figure. Arrows denote thick basement membranes. 72.



Fig. 9. Liver Portal tract with large vessels, nerves and ducts 29

in this laboratory [2]. Cellular proliferation was first observed after three days. At this time, however the cultures displayed signs of a bacterial infection. By removing the contaminated medium and replacing it daily with a medium containing Kanamycin (100 μg/ml medium) for three days, this infection was eliminated.

Chromosome studies were carried out on two different primary cultures and their subcultures. Sixty-five apparently undamaged cells in mitotic metaphase were analysed. Sixty-four of these cells were found to have *forty-eight* chromosomes.

Seventeen 48-chromosome cells were subjected to detailed analysis by inspection in the microscope and with the aid of enlarged photomicrographs. In all of these cells seven large and six small acrocentric chromosomes were found (Fig 13). In one cell which had not been treated with colchicine, satellites were observed on all of the seven large acrocentrics. From the appearance of the six small acrocentrics it was not possible to identify the extra chromosome in this group, i.e. to decide whether it could be a second Y chromosome or an extra autosome of the 1–22 group (Fig 14). Satellites were never clearly visible on more than three of these chromosomes, neither could these small acrocentrics be classified into (21 22) autosomes and Y chromosomes by other morphological criteria.

Summary of findings

Gross pathology Multiple malformations including microphthalmia polydactyly



Fig. 10. Pancreas. Focus of connective tissue containing large ducts and several large vessels (arrows). 29

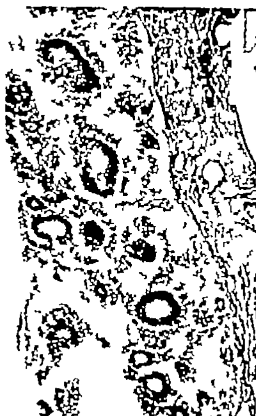


Fig. 11 Eye. Ciliary body with rosett formation. 184

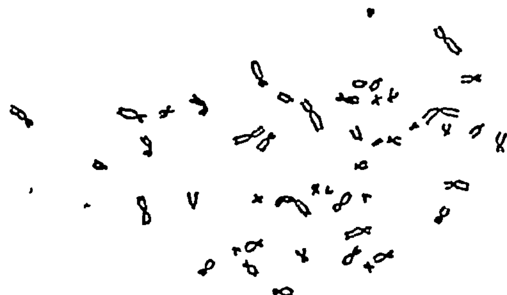
ventricular septal defect and cerebral vascular anomalies

Histology Dysplasia of kidneys, liver and pancreas with evidence of an excess of thin walled blood vessels. Similarly an excessive vascularity of the lungs and to a lesser degree of the myocardium

Cytogenetics Forty-eight chromosomes in cells derived from *in vitro* cultures of bone marrow Tentative classification of one of the extra chromosomes as belonging to group (13–15) Tentative classification of the other extra chromosome as a small acrocentric (group (21–22) or Y)

Comments

The present case shows many of the structural anomalies described in previous examples of (13–15) trisomy [1 20 23]. For this reason one of us (B.I.I) having performed the autopsy suggested a post mortem karyotyping of the patient. The cytological data confirmed a trisomy of the group of large acrocentrics (13–15) (the D trisomy described by Patau *et al*). No attempt was made to classify the extra chromosome according to a particular chromosome pair within this group, as it is generally agreed that the three pairs of



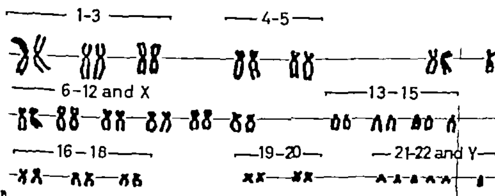


Fig. 12 (A B) Chromosome complement of he proven case 48 chromosomes including one extra chromosome in he group of large acrocentrics (13-15) and one in the group of small acrocentrics (21 22, Y)

large acrocentrics are indistinguishable on the basis of their morphological appear ance in mitotic met phases Assuming that the other xtra chromosom belongs to the group of sm ll acrocentric autosomes it could be either 1 or a 22 Of these two possible trisomies only that of no 21 is est blished as being associated with a spe cific pathological condition, i.e. mongolis As there were no signs or sympt

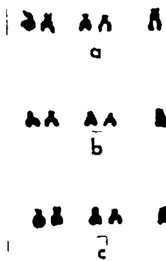


Fig 13. The group of five small acrocentrics of three different metaphase figures from a normal male having an easily identifiable Y chromosome

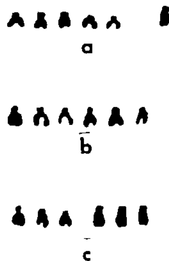


Fig. 14 (a–c). The group of six small acrocentrics of three different metaphase figures from the present case For details see discussion.

this syndrome this possibility appears rather unlikely

A complete or partial trisomy for chromosome no 22 has been suggested by some authors as a possible cause of the Sturge–Weber syndrome [12, 24]. On the other hand, a normal karyotype has been reported in most Sturge–Weber patients subjected to careful cytogenetical studies [9 10 13 18].

One individual, apparently trisomic 22, was reported phenotypically normal [28] In our patient in spite of the presence of malformations of the brain vessels the classical signs of the Sturge–Weber syndrome were absent Even skin hemangiomas, which are apparently characteristic of the D trisomy (13–15) were not present Consequently the phenotypical findings did not help in chromosome identification.

The extra small chromosome may of course be a Y chromosome The three existing reports of individuals with an extra Y chromosome do not suggest any gross morphological effect of this additional chromosome. Two of these patients have been reported to have an XXYY sex chromosome constitution and both were phenotypically similar to the XXY Klinefelter syndrome [5 21] The only individual reported to have simply an extra Y chromosome was a normal male [26] His offspring, however included one child with congenital heart disease a girl with absence of internal sex organs but apparently normal female karyotype and one individual with the common trisomic type of mongolism Consequently it is possible that our patient had an XYY sex chromosome constitution in addition to the D (or (13–15)) trisomy If so one should, of course postulate a disturbance of meiosis other than a non-disjunction during the first division.

Apparently there is no general agree-

ment concerning the criteria for a morphological identification of the Y chromosome. This might be due in part to a certain degree of variability from one individual to another of the size and perhaps also of the centromere position of the Y chromosome. However we feel that in most males it is possible at least in some metaphases, to identify the Y chromosome by its morphological features (Fig. 13). These features are: (1) its size as a rule somewhat larger than that of the chromosomes #1-22, (2) the absence of a satellite, (3) straight chromatids which tend to be more parallel to each other than those of the 21st and 22nd chromosomes, and (4) the difficulty of locating precisely the centromere by a staining gap" and a constriction of the surface contours (Fig 13a). Despite these characteristics, the "identification of the Y chromosomes was very difficult in the present case. Consequently we cannot be certain whether or not an extra Y chromosome is present in this patient. All of the small acrocentrics were of about equal length and, on the basis of the criteria listed above only an occasional single "typical Y chromosome was seen (Fig 14a). In the majority of cells no differentiation was possible. Sometimes only a mere suggestion of the morphological criteria which we believe are characteristic of the Y chromosome could be seen (Figs 14b and 14). The number of satellited small acrocentrics never exceeded three while—according to our present view—five should have been required to demonstrate convincingly the presence of a trisomy of this group.

A general hyperplasia of the blood vessels associated with extra-neural dysplastic changes has been described in the Sturge-Weber syndrome [30]. Our patient does not fulfill the criteria for this syndrome because cutaneous hemangiomas and cerebral calcifications were absent. However an excess of blood vessels in addition to a visceral dysplasia has been observed in familial instances where the renal anomalies, in particular were very similar to those of this patient [15]. The question whether the dysplasia might be secondary to the abnormal vascularization must remain open but our findings and those reported in similar instances of trisomy might indicate that a genetically determined abnormality of the blood vessels has some influence on the growth and differentiation of different organs during embryogenesis. Another finding supporting this view is the generally reduced weight of the visceral organs of our case. This hypoplasia was particularly characteristic of the organs having an excess venous vascularization (kidneys liver pancreas and lungs). There are however several other growth factors involved, e.g the condition of the placenta, which unfortunately was not examined in this case. The patient had two umbilical arteries, which excludes the syndrome of umbilical artery agenesis [3 19].

Hypoplasia of the lungs has been reported in association with renal anomalies by several authors [25]. It has been suggested that underdeveloped kidneys produce small amounts of amniotic fluid which in turn, should diminish the influence of this fluid upon the lungs in utero [..3]. Other authors maintain that the association of malformed kidneys with hypoplastic lungs is coincidental or caused by a common factor. The findings in th

patient could mean that the common denominator is a genetic factor (gene or gross chromosomal aberration) that causes an abnormal vascular system leading to a generalized growth disturbance

Summary

A case of multiple malformations with a 48 chromosome karyotype is described. The malformations included microphthalmia polydactyly ventricular septal defect cerebral vascular anomalies and dysplasia of kidneys liver and pancreas There was a moderate underweight of the visceral organs, most of which showed an excess of blood vessels. The possibility of this increased vasculature being a common denominator of the syndrome is discussed.

The bone marrow cultures used for karyotyping were initiated 7 hours post mortem Analyses showed a probable trisomy (13–15) and in addition an extra chromosome in the group of the small acrocentrics. The identity of the latter was not definitely established but in the absence of signs of mongolism it was thought to be 22 or Y

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(K. H G P E. J.A.B.) Institute for Medical Genetics
University of Uppsala
Uppsala
(B.I.I.) Division of Pediatric Pathology t the Department of Pathology
Karolinska Sjukhuset
Stockholm 60
Sweden

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Listeria Infection in the Foetus and the New born

A Clinical, Pathological and Epidemiological Study

by HANS EKELUND GUNNAR LAURELL, STIG MELANDER, LARS OLDING and BO VAHLQUIST

From the Department of Bacteriology and the Department of Pathology I University of Uppsala, and the Department of Obstetrics and Gynaecology and the Department of Paediatrics, University Hospital Uppsala, Sweden

It was not until the 1950's that human listeriosis became recognized as a not uncommon infection. Attention has chiefly been paid to infection during pregnancy and the neonatal period. Seeliger [21] in particular has contributed to our knowledge of the condition; his monograph has aroused interest in listeriosis throughout the world.

In veterinary medicine the Listeria infections have been well known ever since the organism was accurately described for the first time in 1926 [15]. It may be remembered that the Swedish researcher Hülphers described in 1911 an organism the properties of which, both in culture and in animal experiments, tallied closely with those of Listeria. During the period 1948–60 177 strains of Listeria were isolated from different parts of Sweden at the State Veterinary Medical Institute, Stockholm [10]. Most originated from poultry but other sources included chinchilla, hare, cattle and sheep. A systematic investigation would probably disclose the presence of latent Listeria infection among animals more widespread than has in the past been realized. A considerable reservoir of infection thus probably exists.

The first case of human listeriosis in Sweden was described in 1938 [14], since then roughly 30 more have become known. Most of the patients are newborn infants. In a series of 1250 necropsies on newborn infants carried out at different centres in Sweden listeriosis was given as the cause of death in 1% [13].

In Uppsala the first three cases occurred within a limited period during spring 1959. These have already been published [7, 17]. Because of the limited period during which they occurred and because the patients lived in the same district an epidemiological investigation was started. Attention was drawn to further cases, and routine bacteriological investigations were carried out on pregnant women, premature and full term (healthy) infants, and post mortem material, with the object of detecting Listeria.

This article contains,

1) an account of a series consisting of all children with listeriosis seen in Upp-

ala (and in addition two mothers with the infection) and

*) an epidemiological study carried out on stillborn infants and on selected groups of mothers and live-born infants

Methods

Specimens.—Bacteriological cultures were carried out both on necropsy material and in cases of clinically manifest infection.

The *necropsy material* also included a series of perinatal deaths, described below under the head *epidemiological study* During 1959 the heart-blood, lungs, spleen, kidneys, and gut of these cases were examined; certain exceptions were made when the foetus was grossly macerated. Further the placenta, umbilical cord, and amniotic membranes were examined in all stillbirths. In 1960 the investigations were extended t include also the liver and myocardium, and the placenta, cord, and membranes from all infants dying during the first week of lif were also examined. When special indications were present other material was also examined, for example the cerebrospinal fl id and brain when meningitis was suspected. In addition t cul ture, all organs and placentas were subjected t exhaustive histological investigation.

The post-mortem specimens were col lected by a strictly aseptic and un arying technique Immediately after opening the body specimens were cut from each organ *in situ*, the same part always being taken (e.g. lung tissue from the right lower lobe blood from the right ventricle etc.) New sterile instruments were used for each organ. Large specimens were taken, and treated by Adamson's technique [1], viz., dipped in spirit and then flamed after which they were finely divided in a glass homogenizer Direct cultures and enrichment cultures were then carried out from this homogenate.

Immediately after partus the placentas were placed in steril glass bowls and transported to the Department of Pathology for specimen taking Large pieces were removed close to the attachment of the cord, and treated in the same manner as the foetal organs. Cultures were also made of preparations of amniotic membranes without previous flaming

From the patients with *clinical i fection* specimens were taken from the affected sites; throat and naso-pharyngeal swabs were also taken. Conjunctival secretion was also examined in patient with conjunctivitis. After sampling, the swabs were placed in agar-slope tubes for transportation.

At the same time the patient mothers were also examined, swabs being t ken from the cervix, urethra and vagina. The speci mens were stored and transported in the same manner as the bove Catheter specimen. urine were used for culture

The same technique was used in the *demiological* investigation. Specim meconium and faeces were transpor plastic vessels with no added substanc

In the few animal experiments var organs and blood were examined.

Culture. The following media were used

(1) Sheep-blood-agar plat with tryptose.

(2) Agar plate with 0 04% potassium tel lurite.

(3) Liver–liver broth (Tarozzi)

(4) Dextrose broth with thioglycolate.

(5) Tryptose phosphat broth with furacin 1 100 000 (McBride *et al.* [3])

(6) Incubation at 4°C for one month.

Media 1 and 2 were used for direct culture and 3–6 were used for enrichment. The plates were kept t 37°C, and were inspected on 3 successive days. The enrichment media were inspected for up to 1 days. Secondary cul tures were made on media 1 and in all cases after 12 days, even if no growth was pparent. After incubation in the cold for one month renewed primary culture and cultiva tion were carried out in the same manner

Suspicious colonies were usually first isolated on sheep-blood agar plates, upon which haemolysis was readily apparent For final analysis both biochemical and serological techniques were used. The motility was studied by means of Vahlne U-tube method [23]. In the fermentation experiments we

[Li]steria infections in foetuses and new-born infants

Case no.	Birth-wt.	Clinical signs	Organisms isolated from	Type	Course & sequelae	Necropsy findings	Mother: Clinical signs	Mother: Bacteriological and serological findings
I *Listeria infection with clinical signs or pathological changes compatible with Listeriosis*								
A Organisms isolated in vivo								
1 (EW)	1,590 g	Prematurity + meningit	CSF	2	Hydrocephalus		"Virus" infection	Neg.
2 (AN)	3,100 g	Meningitis + conjunctivitis	CSF naso-pharyngeal conjunctival secretion	1	N sequelae		Vaginal bleeding, upper resp. inf.	Culture pos. Serol pos.
3 (AH)	3,380 g	Attacks of cyanosis + hepatomegaly	Meconium	4 b	No sequelae		Toxaemia	Neg.
B Organisms isolated post mortem								
4 (HJ)	2,330 g	Asphyxia gravis	Visceral organs, blood, placent		Death at 3 hours	Placentitis, pneumonia, granulomata	V ginal bleeding	Raised O-antibody titre
5 (LB)	900 g	Stillborn premature	Visceral organs	2		Placentitis, septicaemia	Impending abortion	Neg.
6 (GO)	610 g	Binovular twin (I), premature, asphyxia gravis	Visceral organs, blood, placenta	1	Death at 1 hour	Placentitis, pneumonia, granulomata	Upper resp. inf. at delivery	Neg.
7 (GO)	625 g	Binovular twin (II), stillborn 15 min after I	Visceral organs, blood placenta	1		Placentitis, septicaemia	Upper resp. inf at delivery	Neg.
II. *Listeria infection with no clinical signs or pathological changes compatible with Listeriosis*								
A Organisms isolated in vivo								
8 (LA)	3,330 g	Healthy	Meconium	4 b	N complications		Healthy	Neg.
9 (EDL)	3,500 g	Healthy	Meconium	4 b	N complications		Healthy	Neg.
10 (UÖ)	3,290 g	Healthy	Meconium	4 b	N complications		Healthy	Not done
11 (SB)	3,500 g	Healthy	Placenta	4 b	N complications		Toxaemia	Not done
B Organisms isolated post mortem								
12 (CN)	675 g	Premature, asphyxia gravis	Liver	3	Death at 1 hour	—	Impending abortion + vaginal bleeding + vaginal discharge	Neg.
13 (AF)	1 820 g	Premature asphyxia gravis, multiple congen. malformations	Placent	3	Death at 1 hour	—	Threatened premature labou	Neg
14 (AJ)	930 g	Binovular win (II), asphyxia gravis	Lung	1	Death 24 hours	—	Pyelitis	Neg.

TABLE 2. *The series arranged in chronological order and with respect to Listeria type*

	1959				1960				1961	
Trimester	I	II	III	IV	I	II	III	IV	I	II
Number of cases	1	2	0	0	2	1	3	1	3	1
Listeria type	2	2,..	—	—	1 1	1	2,2 4b	?	4b, 4b 4b	4b

followed the scheme recommended by Hart gk [8], employing lactose, trehalose rhamnose, aesculine, salizine methyl red, mannite, sorbite, and raffinose Motile strains with typical biochemical properties were typed serologically against the five known types, using Seeliger s tube agglutina tion technique [21]. The 0-antigen alone was determined. Since up to now absorbed sera have not been used, overlapping reactions have been noted to some extent. All but two of the strains in this investigation were kindly confirmed and typed by Dr Seeliger Bonn.

The culture technique was slightly modi fied during the course of the investigation. The figures in brackets in the tables refer t the number of specimens examined by the full technique i.e. including enrichment as in 5 and 6.

Serological investigation. Some ttempts were made t demonstrat antibodies in serum. Seeliger t be-agglutination method wa employed. 0-antibodies only were esti mated.

Clinical Material

Listeria organisms were isolated from a total of 1 foetuses and new-born infants, and from the placenta in two other cases. Clinical and pathological findings fully compatible with listeriosis were made in seven cases, whereas in the remaining seven Listeria was recovered from organs or meconium and placenta although no characteristic changes were present. Two of the mothers showed bacteriological and or serological signs of Listeria infection The whole series is shown in Table 1 and the chronological order of the cases is given in Table ²

Comments

I *Listeria Infection Associated with Cl ni cal Signs or Pathological Findings Compatible with Listeriosis*

A *Listeria organ sms isolated in vivo*

Case 1 This case has been published previously [7]. The patient was girl born 6 weeks before term. The birth weight was 1 590 g She showed no signs of illness t birth, and the first weeks of li were un eventful. The infant then developed purulent meningit s. Listeria organisms of type 2 were isolated from the cerebrospinal fluid She ecovered rapidly on treatment with chloramphenicol, penicillin, streptomycin, and gamma globulin. At the age of 2 months, however she developed progressive hydrocephalus requiring subsequent neurosurgical treatment

The hild mother was a primigravida. During the 7th month of pregnancy she had become acutely ill with pyrexia, headache and signs of meningeal irritation. She was admitted to hospital for 4 days for observa

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Over and above the cases of listeriosis recorded here, only one further case has occurred in Uppsala. This concerned 59-year-old woman with meningo-encephalit s from which she recovered, the tentative diagnosis was made on the basis of serological findings.

tion, and was judged to be suffering from "virus infection" No cultures were made with regard to Listeria, and antibiotics were not given. The child was born weeks after the onset of symptoms. The mother was examined for Listeria one month after her illness. Repeated cultures and serological tests were negative. She again became preg nant 18 months after the birth of the first child. The second pregnancy which was fol lowed losely was uncomplicated No clinical or bacteriological signs of Listeria infection could be elicited and she gave birth to a healthy boy at the expected time.

Case 2 This was a boy born 2 weeks after the expected date *Partus* was normal, and the infant weighed 3 190 g At birth he had a slight nasal discharge but was otherwise healthy On the third day of life he developed pyrexia of 39° but showed no clinical signs of meningitis. Lumbar puncture however disclosed purulent meningitis. Listeria type 1 was isolated from the cerebrospinal fluid, and from the nasal, pharyngeal and conjunctival secretions, but not from the stools Oxytetra cycline, chloramphenicol, and sulphonam ides were immediately given in high dosage (-3 times the usual) Listeria organisms disappeared from the spinal fluid within two days. The infection cleared up without neurological sequelae On re-examination at 18 months of age the patient was perfectly healthy and normally de eloped, and the electro-encephalogram was normal.

The patient's mother was a III para, and had previously borne two healthy children. She had had slight uterine haemorrhage in the 5th month. During the 9th month she had had a prolonged upper respiratory in fection without pyrexia, but this cleared up spontaneously and she was well until de livery when she developed headache and pyrexia lasting 4 hours. Listeria type I was isolated 5 days post partum from the cervix and urethra, but cultures of nose and throat swabs, urine and faeces were negative

Serological tests.—One month after partus —agglutinin titre 1 128, CFT 1 160; 3 months after partus—agglutinin t tre 1 1*8, CFT 1 40; 4½ months after partus—aggl tinin titre 1:1.., CFT 1:120. The mother was then suffering from Listeria infection bacteriologically and serologically established.

Case 3 The patient was a girl weighing 3180 g at birth and born at the expected time Birth was normal, but the amniotic liquor was stained with meconium. At birth the infant was healthy but towards the end of the first day of life she had several brief attacks of cyanosis, during which she suf fered marked respiratory distress, with tachycardia and enlargement of the liver to 5–6 cm below the costal margin. There was no pyrexia or evidence of meningitis. The cerebrospinal fluid was normal, and no or ganisms could be cultured from it or from the blood Treatment with tetracycline and digitalis was started immediately and was continued for 5 days, the child becoming symptom free after 24 hours. Listeria type 4b was isolated from a specimen of faeces taken on the 2nd day of life, after 12 days enrichment in the furazin-containing medium and Tarozzi s liver broth. Follow-up exam ination at 2 weeks of age disclosed nothing abnormal, and new cultures of cerebrospinal fluid and faeces were negative

The child s mother was a primigravida. She had had moderate oedema and albumi nuria during the latter two months of preg nancy but had otherwise been well. Culture of cervical and urethral secretions and sero logical investigations three week after de li very were negative

B *Listeria organisms isolated post mortem*

Definite evidence of Listeria infection was obtained on post-mortem examina tion of two still born infants and of two gravely asphyxiated premature infants that died shortly after birth.

Cases 4 and 5 have previously been report ed in detail [7 17], and will not be described here Concerning the mothers of these two babies, it is worthy of mention that in one the pregnancy was complicated by repeated, slight haemorrhages, and in the other by threatened abortion. In Case 5, in which the

foetus was infected with type- Listeria, the type-2 O-agglutinin titre of the mother serum was raised immediat ly after delivery Cultures of specimens taken at the same time were negative, however

Cases 6 and 7 These were pair of binovular twins born four months before the expected date, and weighed 610 and 625 g respectively Twin no. 1 was severely asphyxiated at birth, and died one hour later whereas twin no. 2 was still-born and macerated. Twin no 1 had pneumonia and multiple intestinal granuloma. Post-mortem examination of the other twin was difficult owing to the maceration, but the same changes were probably present. There was grave inflammation of the placenta and umbilical vessels. Listeria type 1 was isolated in primary culture from the viscera and blood of both foetuses, and from the placenta and amniotic membranes. The mother was quite healthy during pregnancy but had minor upper respiratory disease at the time of delivery Bacteriological and serological investigation of the mother was negative

II Listeria Infection in the Absence of Clinical Signs or Pathological Findings Compatible with Listeriosis

All these cases came to light during the systematic epidemiological studies.

A Listeria organisms isolated in vivo

Case 8 9 and 10 three full-term infants. In each case the mother had been perfectly well during pregnancy delivery had been normal, and the infant had shown no abnormal physical signs on routine examination during the first week of lif Listeria of type 4b was isolated from the meconium in these cases. In Case 8, the organism became evident after three days enrichment in the furacin medium, whereas in Cases 9 and 10 growth was obtained only after one month incubation in the cold. Cultures from two of the mothers were negat ve at follow-up examination after 2 weeks and 3 months respect vely None of the placentas was examined.

Case 11 a girl born t term by normal delivery and weighing 3 500 g. No abnormal physical signs were detected at the usual routine examinations during the first week of life

The mother wa primigravida, and had during the latter weeks of pregnancy shown signs of toxaemia. Listeria type 4b was isolated from the placenta after 3 days enrichment in the furacin medium.

B Listeria organisms isolated post mortem

Case 12 a male foetus born 3 months before the expected date and weighing 675 g The infant wa gravely asphyxiated t birth. Heart sound were heard but spontaneous breathing did not occur Death occurred one hour after birth. N other signs of disease and no malformations were pparent. There was slight injection of the vessels of the placenta and amniotic membranes, but there were no obvious signs of inflammation in the placenta or foetus. Listeria type 2 was isolated from the liver after 3 days enrichment in the furacin-containing medium.

The mother had shown signs of impending abortion during the third month of pregnancy and had had repeated small haemorrhages during the fourth and fifth month and vaginal discharge during the 7th month. Bacteriological and serological investigations of the mother 3 and 6 week post partum were negat ve

Case 13 a 3-week premature male infant weighing 1 630 g The hild had severe asphyxia, and died one hour after birth. H had multiple congenital malformations (syndactyly amelia of the right arm, acrocephalus, and malformations of the ears and urinary passages) Post mortem examination disclosed no granulomatous or other inflammatory reactions Culture of the foetal organs was negative There was no placental inflammation Culture of the placenta resulted in growth of Listeria type 2 after 12 days enrichment in the furacin medium.

The mother of this hild had previously borne tw infants with similar congenital malformations. The first was stillborn.

TABLE 3 *Syst matic bacteriological culture in selected groups of paediatric and obstetric cases.*

Group	Material examined	Time of investigation	Number of specimens	Positive cultures	Case no. (of Table I)
Paediatric cases					
Premature infants with or without abnormal clinical signs	Meconium	Oct 1959 – May 1961	103 (63)	0	
Full term infants with clinical signs	Meconium	Oct 1959 – May 1961	84 (43)	1 (1)	3
Healthy full term infants	Meconium	Oct. 1959 – Feb. 1961	4–4 (219)	2 (2)	8, 9, 10
Obstetrical cases					
Healthy pregnant women	Cervical and urethral swabs; nose and throat swabs	March 1960 – Dec. 1960	5– (16)	0	
Habitual abortions, abortions, threatened abortions	Cervical and urethral swabs	March 1960 March 1961	45 (34)	0	
Complicated deliveries	Vaginal swab, urine placenta, amniotic membranes	March 1960 – M y 1961	50 (50)	1 (1)	11

Figures in bracket give the number of cases investigated by full technique

the second is still alive The mother was admitted to hospital during the last month of pregnancy owing to threatened premature labour No Listeria organisms could be demonstrated in cultures taken 10 days before and 4 days and 3 months respectively after delivery and serological tests were also negative

Case 11

Binovular twin no 2, male weighing 930 g The infant was gravely asphyxiated, but breathed spontaneously for brief periods and died one day after birth No inflammatory reactions could be demonstrated in the foetus, cord or placenta. Listeria organisms of uncertain type were isolated from the lung after 1 days enrichment on the furacin medium. The first twin, born 4 minutes before the second one survived for 12 hours; Listeria cultures were negative.

During the 7th month of pregnancy the mother of these twins had suffered from pyelitis for which she was treated with sulphonamides. No cultures were carried out at that time She was delivered one month later No evidence of Listeria infection could be found on bacteriological and serological investigation of the mother months post partum.

Epidemiological Study

To obtain an idea of the extent to which Listeria occurs among pregnant women and newborn infants, several series of systematic bacteriological cultures were carried out. These embraced

(1) post-mortem material (late abortions and perinatal deaths)
(2) meconium from premature and full-term infants
(3) obstetric material (healthy and ailing pregnant women)

The results of these investigations are shown in Table 3

TABLE 4 *Post mortem bacteriological culture in intrauterine and perinatal deaths*

Organ or material	No. of cultures	Total no of positive specimens	Case no. 4	5	6	7	12	13	14
Lung	100 (24)	5	+	+	+	+	–	–	+
Spleen	85 (14)	4	+	+	+	+	0	0	0
Blood	93 (19)	4	+	+	+	+	–	–	–
Kidney	83 (18)	4	+	+	+	+	0	0	–
Liver	21 (19)	1	0	0	0	0	+	–	–
Myocardium	17 (1)	0	0	0	0	0	0	0	0
Liquor	2 (2)	0	0	0	0	0	0	0	0
Brain	3 (1)	0	0	0	0	0	0	0	0
Placenta	70 (31)	4	–	+		+	–	+	–
Amniotic membranes	55 (29)	2	–	+		+	0	–	0

+ positive culture; – negative culture; 0 bacteriological investigations not carried out
Figures in brackets give the number of cases investigated by full technique

1 *Post-mortem Material*

Late abortions and perinatal deaths

This part of the epidemiological investigation forms part of a larger study on the general incidence of infection in a series of perinatal deaths that one of us (L. O.) is carrying out. Since spring 1959 perinatal deaths in Uppsala have been the subject of detailed bacteriological and pathological investigation, using methods mentioned above. This is to be published separately at a later date. So far (spring 1959 to spring 1961) 101 cases have been examined, including late abortions, still born infants and premature and full-term infants dying during the neonatal period. Listeria organisms have been isolated from 7 cases (Table 4). Four cases showed concomitantly pathological changes compatible with listeriosis (Cases 4, 5, 6, 7) but in the other three (12, 13, 14) no inflammatory reactions were demonstrable. The seven cases are described above with the clinical part of the series.

2 *Meconium*

Premature and full-term infant

Specimens were taken once during the first 24 hours of life from (*a*) premature infants, (*b*) full term infants [illegible] normal physical signs during the first [illegible] of life and (*c*) healthy full term [illegible]

(*a*) *Premature infants* [illegible] hundred infants weighing [illegible] born each year at the Obstetric Department of this hospital. All [illegible] less than 2000 g and [illegible] larger prematures [illegible] fall in weight to [illegible] the first days at [illegible] with abnormal physical signs [illegible] et.), are transferred to the Prema[illegible] Unit of the [illegible] Department [illegible] total number [illegible] whom [illegible] cultures [illegible] during the [illegible]

In no case was culture [illegible]

(*b*) *Full term infants* [illegible] [illegible] signs. At the Obste[illegible]

ment of this hospital a total of about 2200 full term infants are born yearly Of these about 7 % are transferred to the Paediatric Department owing to the presence of abnormal clinical signs either immediately after birth or at some time during the first week of life Such signs include birth injury attacks of cyanosis, fits jaundice pyrexia etc The meconium was examined in 54 such infants and a positive culture was obtained in one case (Case 3)

(c) *Healthy full-term infants* Meconium was collected from a number of healthy newborn infants on a ward for healthy mothers where about 800 infants are treated annually During the period October 1959 to March 1961 inclusive altogether 424 cultures were carried out, and three of these were positive (Cases 8 9 10)

3 Obstetric Material

Healthy and ailing pregnant women

The first three cases of listeriosis in Uppsala occurred during the period March –May 1959 and were of the same serological type type 2 (Cases 1 4 5) Furthermore the mothers of all these patients lived in the same street Cases 6 and 7 too, diagnosed 10 months later came from the same limited area, only one block away from the above but these were of type 1

Bacteriological studies were therefore commenced on a series of healthy pregnant women living in the same district The investigation included 5_ women and took place from March 1960 to December 1960 Swabs were taken from nose and throat and from the uterine cervix when the women visited the ante natal linic during the 10th–30th weeks of pregnancy In no case was positive culture obtained

Forty five women with abnormalities of pregnancy were investigated separately Of these 16 had threatened abortion, six habitual abortion (viz., at least three consecutive spontaneous abortions) and 23 incomplete or complete abortion. Eight women with diverse symptoms (pyrexia of unknown origin, vaginal discharge pyelitis etc.) were also examined as a separate group There were no positive cultures.

Yet another group included 50 mothers whose deliveries had been complicated (prolonged labour premature rupture of the membranes meconium-stained amniotic liquor pyrexia, etc) At the time of delivery cultures were made from vaginal swabs, urine, placenta and amniotic membranes. The placental culture was positive in Case 11 No cultures were carried out on the infant, routine clinical examination revealed nothing abnormal It has been impossible to examine the child again since

Besides the geographical distribution of the cases, chronological periodicity in the appearance of different types of Listeria is also of certain significance in connexion with the epidemiological study (cf Table 2) It was decided at an early stage to perform a limited epidemiological study on animals. Bacteriological investigations were therefore carried out on various food stuffs especially eggs and poultry The findings were entirely negative

Discussion

Listeria infection was demonstrated bacteriologically and/or serologically in 16 cases including the mothers of two affected children.

The bacteriological diagnosis presented

no specific difficulties once it had been realized that Listeria might be present Previously the organism may undoubtedly have been missed especially in specimens where it is not usually to be expected for example nose and throat swabs. It may also be difficult to isolate the organism from specimens in which mixed floras are common, such as, for example the vagina and urethra. Microscopical scrutiny of smears was often not very helpful. Motility and fermentation tests and finally serological confirmation are essential for the establishment of the diagnosis. Serological typing proved valuable in the epidemiological study and should form part of every complete investigation. In the clinically manifest infections bacteria were present in large numbers, and could be isolated on direct culture of specimens from the site of infection, or in the case of post mortem material from most of the visceral organs after only one or two days. In the cases discovered during the course of the epidemiological study the positive cultures were limited to one or two organs; bacterial growth was scanty and became apparent only after enrichment. It is therefore important that the post mortem cultures are comprehensive In order for these slight findings to be of any significance it is essential that all specimens be taken under strictly aseptic conditions Evidence that the technique of specimen taking was good in this investigation is provided by the fact that bout 80 % of the post mortem cultures howed no growth of bacteria whatsoever

Having regard to th scanty incidence of organisms, the choice of enrichment media is important In this investigation we found the furacin-containing to give the best yield. This is probably because better inhibition of irrelevant organisms is obtained with this medium where mixed floras are concerned. Gray s technique of enrichment in the cold also proved valuable

All known degrees of severity of listeriosis are represented in the series, from the grossly affected foetus with early intrauterine death (infantiseptic type") to illness with post-natal onset in which early treatment may lead to complete recovery In addition certain striking findings are described for the first time.

Of the seven infants showing clinical or pathological features compatible with listeriosis two were stillborn and two died within a few hours of birth. Three survived, one of them with hydrocephalus requiring shunt operation (Case 1) whereas the other two have apparently recovered fully (Cases * and 3). All three survivors had received antibiotic and sulphonamide therapy in massive doses at an early stage of the illness

The age of onset varied In Case – there was rhinitis at birth but no serious symptoms appeared until the third day of life It is probable for several reasons that infection took place during birth. the mother cervical secretion gave a positive culture and one of the initial symptoms in the infant was conjunctivitis.

In Case 3 the first clinical signs appeared 4 hours after birth Here the diagnosis wa not fully confirmed, but the clinical findings (meconium-stained amniotic liquor tt cks of cyanosis and enlargement of the liver) in combination with the finding of Listeria in the f eces constitute strong vidence in it favour The illness w quickly cleared up by early tet

cycline treatment. Listeria infection could not be demonstrated in the mother three weeks after delivery. She had shown signs of moderate toxaemia during the latter two months of pregnancy. The child's infection cannot in the absence of fuller evidence be placed in relation to the mother's moderate toxaemia, even though it is to be noted that the pregnancy was not free from complications.

In Case 1 the first clinical signs did not appear until 14 days after birth. The mother's acute infection two weeks before delivery was fully compatible with listeriosis of pregnancy, but no definite evidence was obtained. The negative result of culture in the mother are not definitive since the specimens were not taken until two weeks after the infant's birth. The long interval between birth and the onset of the child's symptoms in this case is striking. The incubation period in human listeriosis is not known with certainty, but may probably be up to as long as two weeks [21]. If the child's illness is to be ascribed to that of the mother, it is probable that infection took place during birth or immediately before.

In seven cases Listeria organisms were isolated from diverse material (liver, lung, placenta, meconium) in the absence of clinical signs or pathological changes compatible with listeriosis. In the case of the post-mortem cultures, the significance of this finding is unclear and further experience is necessary in order to assess it. Since the bacteria were in no case isolated until after enrichment, sometimes prolonged, the possibility of contamination must be borne in mind. There is no evidence that such occurred. All specimens were collected under strictly aseptic conditions and in addition the organs were dipped in spirit and flamed. The very large number of specimens that gave completely negative cultures also indicates that the technique was satisfactory.

It is conceivable that the finding of Listeria is an expression of latent Listeria infection disclosed by the enrichment process, which gives bigger yields than ordinary culture. It is also possible that the infection was so recent that pathological changes had not yet had time to become manifest. The findings would also support the experimental observations made by Seeliger & Plab [22], who were able to induce subacute and chronic Listeria infection in mice. In surviving animals that had made a clinical recovery Listeria organisms were detected in the liver, the only organ they examined; no pathological examination of the liver was described, however. In man, too, evidence, chiefly serological, that Listeria infection may run a subacute or chronic course has been published [11, 12, 20]. As far as we know, however, no human case has previously been described in which the organisms have been demonstrated in the absence of pathological changes.

In two cases (Cases 11 and 13) Listeria was isolated only from the placenta. The findings are difficult to assess. An infection may reach the placenta either via the blood or ascending from the genital tract and via the amniotic liquor. Theoretically it would be possible for the picture described, of the presence of bacteria in the absence of inflammation, to occur at a very early stage of the infection.

In the three cases in which Listeria of type 4b was isolated from meconium (Cases 8, 9 and 10), no clinical signs whatsoever

being present in either mother or child, the possibility of contamination with dust was discussed, but was considered un likely A heavily infected environment should be reflected in a larger number of positive cultures. It is a fact that the meconium usually contains bacteria at the time of birth, even though these are comparatively few in number and the flora is mixed [4]. The presence of Listeria in the meconium of healthy newborn in fants has to our knowledge never before been reported, and such a finding has always previously been believed to be associated with abnormal clinical signs in the infant [*].

The number of Listeria organisms in the positive meconium cultures was in all instances low and the bacteria became appar ent only after enrichment. As a rule they were isolated so late that the result never influenced the clinical regime dopted. And it cannot be regarded as established that the positive results of culture in these cases were an expression of actual infec tion in the child. In the light of this it is reasonable to conclude that routine testing of the meconium in cases such as these would be of little value Routine cultures should at present be carried out in cases with clinical signs suggestive of listeriosis or other unclear infections, in which the number of bacteria is probably greater and isolation can be achieved more quickly

In the cases in question, in which Listeria was recovered from the meconium cultures of swabs from the mothers birth canals were negative 3 weeks to 3 months later It is possible though not very probable that infection of the meconium could in some cases have occurred via the placenta without simultaneous infection of the foetus. The pla centa was not examined in any of these cases, and it is therefore not known whether any inflammatory changes were present in that structure

As has been mentioned above the diag nosis of Listeria infection of foetus and newborn infant was in all cases made on the basis of bacteriological findings. In one of the two mothers the diagnosis was based solely on a significant increase in the 0-agglutinin titre to the Listeria type recovered from the infant It is worthy of note that 9 of the 13 mothers of Listeria infants suffered obstetric complica tions during the pregnancy and that seven of these were of such nature that they could have been caused by infection with Listeria. The series is small, and no con clusions may be drawn over and above those directly justified by Cases 1 and 2. The series includes two pairs of binovular twins In one pair both foetuses were shown to be infected (Cases 6 and 7); in the other only one of the foetuses (Case 14) was affected The diagnoses were made on the basis of positive bacteriological find ings in specimens of lung tissue that showed no inflammatory changes at post-mortem examination.

The types of Listeria isolated varied. Type 1 was found in three cases type 2 in five cases and type 4*b* in five cases. The organisms from Case 14 are not yet typed with certainty As already men tioned, the various types have hown some chronological periodicity but the meaning of this is not readily apparent.

In the "complicated delivery" group one positive case was noted (involvement of the placenta). But the epidemiological studies on healthy and ailing pregnant

women were entirely negative These findings differ from those reported by Rappaport *et al.* [19] from Israel, and would suggest that Listeria infection in our part of the world is unimportant as a cause of abortion and habitual abortion (cf also Gray [5])

In the past, extensive epidemiological studies have been carried out among animals, but only rarely in man. Serological studies have indicated that the incidence of Listeria infection in an unselected adult population is about _ % whereas the incidence has been stated to be much higher in series of children with organic nervous disease of uncertain nature [12]. The value of positive serological findings as evidence of Listeria infection is debated however [18]

Systematic, bacteriological, and morbid-anatomical studies are reported by Hood [9] in a recent investigation carried out in New Orleans. The positive findings were few The authoress concludes that,

the cases of listeriosis in this area represent incidental infections rather than clinical manifestations of an underlying endemic centre of disease" The same conclusion is probably justified with regard to the Uppsala district At the same time both the studies here reported and many other more recent ones show that listeriosis is an important problem primarily for the attention of paediatricians and obstetricians In all cases of late abortion, perinatal death or grave infection of uncertain nature listeriosis must be borne in mind. By early treatment with antibiotics it is possible to save the lives and even the health of some of the infants infected in the latter stages of gestation and during birth. It is probable that closer attention to and effective treatment of unidentified pyrexia and other symptoms among pregnant women might save the foetus even in infections occurring during earlier pregnancy [?1]

Summary

In Uppsala during the ? year period 1950–1961 Listeria infection has been demonstrated in 16 cases of mothers and infants (12 foetuses and newborn infants, the mothers of two of these and in a further two cases in the placenta only) It is particularly striking that two of the foetuses from which Listeria was isolated post mortem showed no inflammatory changes and that three symptom free full-term neonates out of a total of 424 examined were found to have Listeria in the meconium

Epidemiological studies were carried out on 6 different groups of cases. The number of individuals examined and the positive findings were as follows.

I One hundred and three premature infants (none positive) II Fifty four newborn full term infants with unexplained clinical signs (one positive) III. Four hundred and twenty four newborn full term infants with no abnormal physical signs (three positive) IV Fifty two healthy pregnant women (none positive) V Fifty women whose labours had been complicated (positive culture of placenta in one case). VI Forty-five women with abortion (none positive)

The results show that human listeriosis is not endemic in the Uppsala area but that it represents a problem of such importance that paediatricians and obstetricians must constantly bear it in mind.

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(H E. and B V) Department of Paediatrics
(B M.) Department of Obstetrics and Gynaecology
University Hospital
(G L.) Department of Bacteriology
(L O) Department of Pathology I
University of Uppsala
Uppsala
Sweden

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REVIEW ARTICLE

Hereditary Ectodermal Dysplasia of Anhidrotic Type

A Report of Three Cases in Boys Aged 3–4 Months

by H. G. JESPERSEN

From the Paediatric University Clinic (Head: Professor Bent Andersen, M.D.), Aarhus Kommunehospital, Aarhus, Denmark

Hereditary ectodermal dysplasia of anhidrotic type is a condition with defects of the tissues of ectodermal origin, principally characterized by anhidrosis, hypotrichosis and hypodontia. Although it is rare the condition has been described so often and uniformly that it must be conceived as a well-defined disease entity Kaalund-Jørgensen & Flamand Christensen [11] collected 60 cases and Perabo *et al.* [20] 130 cases from the literature In 1950 Bernard *et al.* [9] claimed to know of a total of 244 cases. The disease has been reported from many different parts of the world, but only a few cases are on record in the Scandinavian medical literature [9 11 15 21 24]

Most of the reported cases were observed in older children or adults A characteristic feature which is mentioned in all case *histories* is the discomforts caused to the patients by the absence of sweat glands. As the defects are congenital intolerance of heat is present from birth and it is therefore surprising that the disease is only rarely reported to be the cause of hyperpyrexia in infants. In reviewing the literature I was able to trace only seven instances in infants under 6 months [2, 6 8 14 18 23]. The explanation probably is that the presence of trivial *infections* may easily be conceived as a plausible cause of the frequent attacks of fever occurring in such patients.

The cases reported below illustrate the diagnostic difficulties to which this assumption and the rarity of the disease may give rise

Case Reports

Case 1

A boy J K. (90/53) aged 3 months, was admitted to hospital on Nov. 28 1953. H was the younger of two children. His elder sister was reported to have eczema; otherwise the family was healthy

The patient was born at term; the delivery was normal, birth weight 3775 g. It was noted at birth that the skin was strikingly thin and translucent and eczema of the face and scalp was present The boy thrived well and showed no signs of disease during the first [illegible] months of life He then caught a c[illegible] accompanied by high-grade fever which disappeared within [illegible]4 hours after treatment

with sulphonamides. A few days later fever recurred, and the boy was admitted to a local hospital; as signs of pneumonia were present, the patient was treated with antibiotics. Within the next few weeks several attacks of fever (up to 41°C) of sudden onset and lasting only a few hours occurred. During the attacks, the patient was acutely ill, with greyish pallor of the skin, distended abdomen, opisthotonus and convulsive movements of the limbs. The spinal fluid revealed 3 cells per ml and an increased content of protein. In view of these alarming symptoms the *patient was transferred to the* Pediatric University Clinic, Aarhus Kommunehospital.

Physical examination on admission revealed a poorly nourished, acutely ill infant with diminished turgor and sparse subcutaneous tissue. The face was suggestive of that of an old man. The eyes were slightly protruding; the skin of the eyelids was finely wrinkled. The external ears were deformed, somewhat creased. The nasal airway was partially obstructed by secretion. The growth of hair was sparse. The voice was thin and flat. The nails were normal. The rest of the physical examination was non-contributory.

Laboratory findings. The urine did not contain protein or sugar and showed no microscopic abnormalities. Haemoglobin 84%; blood urea 40 mg/100 ml. The Moro and Widal tests were negative. The spinal fluid revealed admixture of blood, the Wassermann reaction was negative. On a subsequent examination the spinal fluid was found to be normal.

During *2-month stay in* hospital the patient had frequent attacks of fever up to about 41°C associated with restlessness, rapid and superficial respiration and intense redness of the skin. The attacks disappeared promptly as soon as the patient was stripped, and it was recorded that these reactions seemed to be referable to heat.

During the hospital stay pneumonia developed; it subsided after treatment with aureomycin. Otherwise the episodes of hyperpyrexia were not accompanied by evident signs of pneumonia or other infections.

Our only diagnosis was one of fever of unknown cause. As the condition apparently improved, the boy was sent back to the local hospital, where death occurred a few days later in hyperpyrexia.

Case 2

A boy J. K. (758/56), aged 3 months, was admitted to hospital on April 23, 1956.

H. was the youngest of three children and a brother of the aforementioned patient. It was now stated that the sister lacked some teeth, and that the mother and grandmother were thin haired, but that they perspired normally.

The patient was born at term; the delivery was normal; birth weight 4400 g. During the first few weeks of life he thrived normally, but then periods of restlessness, crying and fever began to occur. Nasal obstruction was noticed, and small papules on the face were observed. H. was admitted to a local hospital, where the condition was still characterized by restlessness, definite malaise and frequent attacks of fever of short duration, accompanied by intense redness of the skin of the nuchal and occipital regions. As the cause of these reactions could not be demonstrated, the patient was transferred to the Pædiatric University Clinic, Aarhus Kommunehospital.

Physical examination. On admission the patient revealed a striking resemblance to his brother. H. could smile and fix his attention on objects and persons, and raise the head when placed in the prone position. H. was alert, and it was easy to make contact with him. Marked spontaneous muscular *activity was noticed. His facial appearance* was suggestive of that of an old man. The scalp hair was soft and fine in texture, fair and sparse. Eyebrows were absent, and the eyelashes consisted of only a few scattered hairs. The eyes were protruding and the skin of the eyelids was thin and wrinkled. The external ears were asymmetrical. The nose was obstructed, and an ozaena-like smell was noticed. There were red, scaly papular lesions on the scalp, but no other

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REVIEW ARTICLE

Hereditary Ectodermal Dysplasia of Anhidrotic Type

A Report of Three Cases in Boys Aged 3–4 Months

by H. G. JESPERSEN

From the Paediatric University Clinic (Head: Professor Bent Andersen, M.D.), Aarhus Kommunehospital, Aarhus Denmark

Hereditary ectodermal dysplasia of anhidrotic type is a condition with defects of the tissues of ectodermal origin, principally characterized by anhidrosis hypotrichosis and hypodontia. Although it is rare the condition has been described so often and uniformly that it must be conceived as a well-defined disease entity Kaalund-Jorgensen & Flamand Christensen [11] collected 60 cases and Perabo *et al* [20] 130 cases from the literature In 1959 Bernard *et al* [2] claimed to know of a total of 244 cases. The disease has been reported from many different parts of the world, but only a few cases are on record in the Scandinavian medical literature [10, 11 15 21 24].

Most of the reported cases were observed in older children or adults A characteristic feature which is mentioned in all case histories is the discomforts caused to the patients by the absence of sweat glands As the defects are congenital intolerance of heat is present from birth and it is therefore surprising that the disease is only rarely reported to be the cause of hyperpyrexia in infants. In reviewing the literature, I was able to trace only seven instances in infants under 6 months [–, 6, 8, 14 18 23] The explanation probably is that the presence of trivial infections may easily be conceived as a plausible cause of the frequent attacks of fever occurring in such patients.

The cases reported below illustrate the diagnostic difficulties to which this assumption and the rarity of the disease may give rise.

Case Reports

Case 1

A boy J. K. (90/53) aged 3 months, was admitted to hospital on Nov 23, 1953. He was the younger of two children. His elder sister was reported to have eczema otherwise the family was healthy

The patient was born at term, the delivery was normal, birth weight 3775 g It was noted at birth that the skin was strikingly thin and translucent and eczema of the face and scalp was present. The boy thrived well and showed no signs of disease during the first months of life He then caught a [illegible] accompanied by high-grade fever which disappeared within 24 hours after treatment

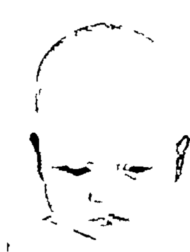


Fig. 3. Case 2, age 4 months.



Fig. 4. Case 3 age 4 months. Radiograph of facial bones showing cone-shaped unerupted teeth in the maxilla.

clinic revealed a normally nourished boy. H could walk unsupported, was interested in his surroundings, and could say "yes" and "no". As before the facial expression was much like that of an old man. The hair was thin and sparse: the skin was of an atrophic appearance: the nose was flat and broad, and the lips were thick and somewhat protruding.

As before frequent febrile episodes occurred, with eruptions of petechiae on the thighs and buttocks. A diagnosis of hereditary ectodermal dysplasia of the anhydrotic type was then suggested for the first time. Supplementary radiographic examination of the jaws showed complete anodontia of the mandible and that only three teeth were embedded in the maxilla (Fig. 2). Sweat test or skin biopsy was not performed.

On request, the family doctor informed us in August 1961 that the boy was fairly well, but that febrile episodes of sudden onset still occurred, and that he spontaneously sought out cool, shady places.

Case 3

A boy H. J. (*97/61) aged 4 months, was admitted to this clinic on June 10, 1961.

He was the youngest of six children. The other siblings were all boys. Four were in good health, while one had died. This fifth brother had had attacks of fever of short duration; otitis media had developed, and he died in hyperpyrexia, possibly from a cerebral abscess.

Our patient had been in good health during the first three weeks of life; then fever suddenly developed, and the boy was admitted to a local hospital, acutely ill and dehydrated. Stools were frequent and thin. The condition improved after fluid therapy but during the next few months steep rises in temperature followed by equally steep falls occurred. Pneumonia developed, but apart from this no obvious signs of infection were observed and treatment with various antibiotics did not change the condition. Chest radiography revealed atelectasis of the right apical region. A number of laboratory examinations failed to give any definite information, and in view of the obscure clinical picture the boy was transferred to the Paediatric University Clinic, Aarhus Kommunehospital. On admission here one of the nurses at once noticed the striking similarity to the two aforementioned brothers (with whom he was unrelated).

Physical examination on admission revealed a flaccid and weak boy who was not acutely ill. The facial expression was that of an old man. The scalp hair was sparse fair and soft The eyebrows and eyelashes were very sparse otherwise there was no growth of hair The skin was smooth, dry and thin; that of the eyelids finely wrinkled Slight pigmentation was noted. The lips were thick, but the tongue was normal Auscultation of the lungs revealed *signs of an infiltrate in the* right apical region. The liver was palpable two fingerbreadths below the costal margin The rest f the physical examination was non-contributory (Fig 3). The boy could smile fix his attention on objects and persons and was often babbling

Laboratory find gs. The urine was negative for protein and reducing substances and appeared normal on microscopic examination. The Moro test was negative; haemoglobin 95%.

Chest radiography revealed an intumescence in the right pical region, which in special exposures appeared to be the thymus.

During the hospital stay several attacks of hyperpyrexia occurred without any apparent cause; these were accompanied by malaise restlessness and rapid superficial respiration, but the boy did not cry

In order to confirm the suspicion of hereditary ectodermal dysplasia f the anhidrotic type the j ws were examined radiographically which revealed retarded dental development (Fig 4). Sweat test with the iodine–starch indicator described by Minor [17] were performed, first by warming under a light arc, which did not result in an increase in the body temperature Secondly the patient was heavily clothed and packed into a woollen blanket which resulted in a rise in rectal temperature to 39°C within 15 minutes. During a spontaneous rise in temperature to 39.8°C the boy was finally given 250 mg acetylsalicylic acid, which resulted in a fall in the body temperature to 37.2°C within 90 minutes. During these test no perspiration at all was bserved in any region of the body

Skin biopsy The epidermis was normal but a fairly large number of sections failed to reveal any sweat glands, sebaceous glands or hair follicles. The corium was relatively thin, with irregular and irregularly arranged collagen fibrils. The larger vessels and capillaries were normal. As compared with that of the collagen tissue, the amount of elastic tissue seemed to be normal, but the elastic fibres showed some irregular arrangement The subcutaneous tissue showed no abnormalities *(Dr Tage Lund).*

On being questioned, the mother stated that she and her two sisters were thin-haired, but had normal teeth. They were able t perspire but not profusely Each of the two sisters had a son. These two boys had both been admitted to hospital with hyperpyrexia of sudden onset occurring without any pparent cause. The skin of one f the boys was described as delicate" The other boy had a facial appearance like that of an old man; he was lean, slender with a dry parchment like skin. He had no eyelashes. H had undergone an operation for a malignant mediastinal tumour

Nothing seems t be at variance with the assumption that both these boys suffered from the same disease as our patient and it must be presumed that our patient s brother who had died also had the same disease The maternal grandfather of these children is alive and in good health.

Symptomatology

In 1848 Thurnam [–5] described two cases in which the skin hair and teeth were very imperfectly developed Darwin [6] mentioned a Hindu family observed by Wedderburn about 1838 Many of the male members of this family had only a few scattered teeth became bald at an early age and suffered great discomfort in the heat and sun because of an excessively dry skin. In 1929 Weech [*0] traced about 10 cases of the same nature in the literature He was the first to realize the

constant characteristics of the disease and called attention to the fact that it might be divided into two main groups. One group was characterized by inability to perspire while the other group of patients who had sweat glands revealed characteristic deformities of the nails. A feature common to both groups was the defective development of the hair and teeth. Weech suggested the term which is now in common use, viz. hereditary ectodermal dysplasia, and that the disease should be subdivided into an anhidrotic and a hidrotic type. The latter type seems to be far more frequent than the former. Since then, a large number of case reports have appeared in the literature, and several comprehensive surveys have been published [7 10 11 20].

Anhidrosis Clinically this is the most important symptom. The inability to perspire gives rise to abrupt rises in the body temperature when a surplus of heat is to be eliminated, or the external temperature is high. It is reported how the patients must stay indoors in summer, must take cool baths, avoid hot drinks etc. When in the field, a farmer had to be accompanied by a boy who poured cold water over his clothing at short intervals. Such reports show that adults and older children learn how to manage with this anomaly but it cannot be doubted that the anhidrosis may endanger the lives of affected infants if the nature of the disease is not recognized.

The absence of sweat glands is usually complete although sparse rudiments have been observed [22]. Kline *et al* [12] applied a sweat test utilizing the change in the electric resistance of the skin on perspiration. This test is claimed to be very sensitive and by its application the authors revealed absence of sweat glands in smaller or larger areas of the skin in some apparently normal members of a family affected by ectodermal dysplasia of the anhidrotic type.

Hypotrichosis After puberty axillary and pubic hair is usually present but otherwise the anomalous hair growth is most pronounced on the trunk. The scalp hair is thin, fair and soft and lanugo hair is sparse. In the adult male facial hair is usually present. Eyelashes are scanty and eyebrows are absent in most cases. The deficient hair growth is mainly of cosmetic importance.

Hypodontia This anomaly is not only of cosmetic significance as it often reaches severe degrees; [illegible]ctive dental treatment is both possible and required [15 22]. A varying number of both deciduous and permanent teeth may be absent, and cases associated with complete anodontia have been described. The teeth present are often impossible to identify. Thus, in the front of the mouth there are often a few cone-shaped teeth resembling canines. In the absence of tooth buds, also the alveolar processes fail to develop. This defect may be observed before the eruption of teeth which is usually greatly delayed.

Other signs Certain additional features usually contribute to the characteristic appearance of the patients. The lips are often thick and protrusive which is partially due to the absence of alveolar processes. This is conducive to the characteristic facial expression suggestive of old age. The skin is described as delicate translucent smooth thin and dry and is often the site of papular lesions or eczema. The pigmentation of the skin seems to

vary but lack of pigment is very common. The eyelids are thin and wrinkled, and prominence of the supra-orbital ridges is sometimes a characteristic feature.

Atrophic rhinitis is often present; the voice is hoarse lacrimation is diminished and the mammary glands are hypoplastic

Mental deficiency has been described in association with ectodermal dysplasia but in most cases it is reported that the patients are of normal intelligence Consider ing the common occurrence of mental deficiency caution should be exercised in deducing an aetiological relationship between these two conditions. Incidentally defects in the central nervous system have never been reported, although this system is also of ectodermal origin Petechiae, which occurred in our second case have been described in only one previous case [19]

Diagnosis The little old man" with scant lanugo hair thick lips, complete or partial anodontia and intolerance of heat represents a characteristic clinical picture The triad of anhidrosis, hypotrichosis and hypodontia is of crucial importance in the diagnosis. Hypodontia and hypotrichosis may occur separately and either may be associated—alone or in combination—with other symptoms in a number of related conditions of which Franceschetti [7] has given a brilliant survey Among these conditions, the hidrotic type of ectodermal dysplasia is the most frequent and the one which has most features in common with the anhidrotic type

Anhidrosis as an isolated phenomenon (in association with neurolabyrinthitis) has been described only in one family by Helweg Larsen & Ludvigsen [9].

If information of familial occurrence is available the diagnosis should not present difficulties. However in infants, isolated cases may undoubtedly easily be over looked. Thus, in our first case we did not make the proper diagnosis until the younger brother was admitted with the same clinical picture

Differential diagnosis. The signs and symptoms may to some extent be suggestive of congenital syphilis, but this diagnosis does not agree with the fact that only tissue of ectodermal origin is affected. Clinically no relation to this infection has ever been demonstrated

Hypothyroidism may lead to dry skin, sparse growth of hair and hoarseness. However this condition is also accompanied by retarded development of the centres of ossification and, in congenital cases, by mental retardation and dwarfism. Protein bound iodine which is low in hypothyroidism, was found to occupy a normal level in our second case No other reports on protein bound iodine seem to be available in cases of ectodermal dysplasia Therapeutic experiments with thyroidin did not exert any definite effect on the anhidrotic type of dysplasia [9, 10]; on the contrary administration of thyroidin may lead to life-threatening hyper pyrexia [10]

Wilkins [27] writes that idiopathic hypoparathyroidism may result in changes in the skin and hair growth similar to those observed in ectodermal dysplasia, but that disturbances in calcium metabolism are absent in the latter condition.

Progeria exhibits the same facial appearance of old age as is seen in ectodermal dysplasia and is also associated with thin skin and sparse hair growth On the other hand, progeria is not hereditary or ac

companied by anhidrosis, but it results in dwarfism and leads to arteriosclerosis, senility and death at an early age.

In considering a diagnosis of ectodermal dysplasia of the hidrotic type most authors recommend that it should be ensured that the anomalies of the hair and skin are not referable to a mycotic infection.

Heredity Ectodermal dysplasia is a heredofamilial disorder occurring mainly in males Franceschetti [7] reported a male-to-female ratio of 105/15 In many families, the disorder seems to be transmitted by normal women to their sons, which is suggestive of an x-chromosome-linked, recessive mode of inheritance In other families there are affected females, and Cockayne [4] expressed the view that in these families the disease is inherited as an autosomal dominant. Levit [13] suggested that there may be an x-chromosome-linked incomplete dominance A final proof of an autosomal mode of inheritance would be that the disease was transmitted directly from a father to his son. The few cases in which this has been observed were atypical and differed on several points from the condition described here [1 3 9] Apparently it is still a common assumption that the disorder is an x-chromosome linked character possibly recessive in some families and irregularly dominant in others. The case reports presented in this paper do not contain any features which are at variance with this assumption.

Treatment Causal treatment is obviously not possible. Dental treatment should be instituted at an early age In view of the intolerance of heat some vocational guidance is desirable In infants it is important that the condition is recognized as early as possible so that they can be protected against hyperpyrexia whereas experience shows that older children rapidly learn how to take measures against rises in body temperature

Prognosis Experience gained in adults seems to show that ectodermal dysplasia is without definite importance in the general state of health and life expectancy On the other hand, it cannot be doubted that the attacks of hyperpyrexia actually endanger the lives of affected infants. Bernard *et al* [2] reported a case which shows that this may also apply after the proper diagnosis has been made

Summary

Three cases of hereditary ectodermal dysplasia of the anhidrotic type occurring in boys aged 2–4 months are reported. The disease manifested itself principally by attacks of hyperpyrexia. Much consideration was given to the possibility of infectious disease in our first case the correct diagnosis was not established until a brother later presented the same symptoms The syndrome is described on the basis of the literature and our own experience The triad of anhidrosis, hypotrichosis and hypodontia is of decisive diagnostic importance Heredity is briefly mentioned. The syndrom is probably inherited as a sex linked recessive or in some cases incomplete dominant character Early diagnosis is of great importance in order to protect affected infants against the hazard involved in hyperpyrexia.

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Paediatric Department
Kommunehospitalet
Aarhus
Denmark

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SUMMARY OF SUPPLEMENTS

The Relation of Linoleic Acid to Infant Feeding

A Review

by ARILD A HANSEN M.D., Ph. D ROBERT A. STEWART Ph. D., GERTRUDE HUGHES, A. A., and LARS SÖDERHJELM, M.D

(Supplement 137)

Although it has been known for longer than three decades that experimental animals do not synthesize linoleic acid, which must therefore be supplied in the diet, unequivocal evidence that the human infant does not thrive when his diet lacks this nutrient has been brought forth only recently The demonstration of the development of abnormality in dermal structure impairment of growth and apparent limitation of caloric efficiency and of the reversal of these conditions by the addition of this specific unsaturated fatty acid to the infant s diet strongly supports the concept of its essentiality The relationship of the appearance and reversal of similar histologic aberrations to sufficiency or deficiency of linoleic acid in diets of experimental animals supports this concept.

Renal lesions resulting from a deficiency of fat have not been known in the human subject, however nor has any relation to fecundity been observed such as has been noted in the laboratory animal. Increased oxygen consumption one of the first metabolic abnormalities to appear in some laboratory animals when on diets deficient in linoleic acid has not been demonstrated in human infants.

Recognition of the essential nature of linoleic acid in infant feeding has come comparatively late because even relatively small amounts exert a protective effect. The discovery of the essential nature of fat required the development of highly purified fat-free diets (first expressed as the "rigid" exclusion of fat) for use in the experimental laboratory Further reasons for the slow realization of the importance of linoleic acid in the diet of the human subject includ

1 A completely fat free diet is difficult to obtain under natural living condi tions.
2 Natural foods (milk of various susceptible species) contain fat having sufficient linoleic acid for the particular species
3 Cereal grains, which are fed to infants early in life although low in total fat are high in linoleic acid content hence are suitable additions to the infant diet.

4. Degree of severity of manifestations depends upon rate of growth.
5. Failure to grow precludes the possibility of development of the dermal manifestations of fat deficiency

Most helpful in adding to the understanding of the importance of linoleic acid in human nutrition has been the study of the blood serum levels for the di tri- and tetraenoic acids—especially study of the first While minimum optimum, or maximum linoleic dietary requirements for the human infant remain unascertained, there is enough background for several conjectural statements until more exact methods of measurement definitively settle the problem.

A. In the natural method of feeding infants—mother's milk—some 4 to 5 per cent of the calories are present as linoleic acid, an amount dependent upon the nature of the maternal diet.

B Infants thrive well when given cow's-milk formulas from which they receive approximately 1 per cent of their calories as linoleic acid.

C Use of artificial milk mixtures from which butterfat has been removed and replaced with various vegetable oils and animal fats varying considerably in linoleic acid content has likewise been found to be satisfactory for infant feeding

D The dienoic acid level of the blood serum for infants receiving breast milk, cow's-milk formulas or artificial mixtures whose butterfat has been replaced with vegetable oils containing liberal amounts of linoleic acid are respectively 20-25, 10-12 and 30-40 per cent of the total fatty acids of the serum.

E. The dienoic acid level of the blood serum in infants evidencing fat deficiency is in the neighborhood of 5 per cent of the total fatty acids; levels as low as 1 to 2 per cent of the total fatty acids have been found in infants fed on milk mixtures almost devoid of fat.

F Dienoic-acid blood-serum levels between 5 and 10 per cent of the total fatty acids seem to be between inadequate and minimal normal levels.

G Characteristic of the fat-deficiency state are high levels for trienoic acids and low levels for tetraenoic acids in the blood serum.

Despite the inconsistencies and incompleteness of observations with human subjects and studies with experimental animals it appears advisable to exercise caution in prescribing prolonged use of diets low in fat and low in linoleic acid. The decision regarding optimum intake awaits further careful studies, as has already been indicated, although it may well be that the limits are rather broad. This decision regarding the ideal intake will concern not only current needs of the infant, but also ultimate requirements for an ideal nutritional state throughout childhood and for the best possible state of health in later years.

Pulmonary and Renal Circulation in Children with Patent Ductus Arteriosus

Pre- and Postoperative Studies of Thirty Four Cases

by ERIK IVAR WALLGREN

(Supplement 138)

The influence of a patent ductus arteriosus on pulmonary and renal hemodynamics was studied pre- and postoperatively in 34 children, ranging in age between 7 and 15 years.

In all patients right heart catheterization was performed, including measurements of pressures, flows and vascular resistances in the pulmonary and sytemic circuits. The renal clearances of para amino-hippurate and true endogenous creatinine were determined. About eight months after surgery the same investigations were repeated in every case except one who died postoperatively

Preoperatively the pulmonary arterial pressure was normal in 22 children. In 1* children the pulmonary arterial systolic pressure exceeded 25 mm Hg, and these cases were considered to have pulmonary hypertension. In one girl the pressure in the pulmonary artery almost equaled that in th aorta This patient died postoperatively

Recanalization of the ductus occurred in seven patients, all of whom had pulmonary hypertension These cases were reoperated, and in four the aforementioned investigations were performed once more Thus, altogether 71 determinations of the cardiopulmonary and renal hemodynamics formed the basis of the present study

The systemic blood flow measured by the Fick method was normal in the majority but low in a few of the cases studied The mean systemic arterio-venous oxygen difference was normal in the patients with normal pulmonary arterial pressure In the children with pulmonary hypertension this difference was usually higher which was possibly due to a slightly decreased systemic blood flow Determinations of the oxygen saturation in the superior and inferior venae cavae suggested that this decrease of systemic blood flow involved equally the upper and lower parts of the body There was a slight positive correlation between the arterio-venous oxygen difference and the size of the shunt through the ductus.

The correlation between the external diameter of the ductus measured at operation, and the shunt through the ductus was better when the shunt was expressed in per cent of the left ventricular output than when the shunt was measured in absolute flow units.

Prior to operation the systemic systolic and mean blood pressures were lower in the cases with pulmonary hypertension than in the cases having normal pulmonary arterial pressure Despit this no change of the resistance to flow in the peripheral vascular bed could, on an verage

be established following closure of the ductus

Pulmonary hypertension, when present, was caused by one or several of the following main factors high pulmonary venous pressure elevated vascular resistance or increased blood flow High pulmonary venous pressure was probably the least important of these factors No correlation was found between the PCV pressure and the pulmonary arterial pressure In all cases the PCV pressure dropped to normal after closure of the ductus.

The pulmonary vascular resistance was high in all patients with a preoperative pulmonary arterial systolic pressure exceeding 60 and a mean pressure exceeding 45 mm Hg The increased pulmonary arteriolar resistance and total pulmonary vascular resistance did not on an average decrease after closure of the ductus. The elevated pulmonary arterial pressure decreased postoperatively mainly as a result of reducing to normal the blood flow through the lungs

In all patients having before operation a normal pulmonary arterial pressure the pulmonary arteriolar resistance was below normal and increased significantly after surgery

A close relationship between the flow through the ductus and the pulmonary arterial pressure was observed preoperatively In all the cases with shunts of more than 60 per cent of the left ventricular output the pulmonary arterial pressure exceeded normal values If the systolic pulmonary arterial pressure was higher than 70 mm Hg, the shunt tended to decrease as a result of marked elevation of the pulmonary vascular resistance After recanalization of the ductus this relationship between the shunt and the pulmonary arterial pressure changed. The pulmonary arterial pressure remained at a higher level than in unoperated cases with shunts of corresponding sizes.

If the shunt was smaller than about 30 % of the left ventricular output the heart volume was normal. With larger shunts a positive correlation between heart volume and the shunt was observed.

The hematocrit did not differ in cases with either normal or elevated pulmonary arterial pressure After operation the mean hematocrit increased in both groups.

The renal clearance for para-aminohippurate was on an average low before closure of the ductus. Definitely low figures were observed in two cases with normal and in two cases with elevated, pulmonary arterial pressure The low effective renal plasma flow was probably not related to high renal venous pressure since the right atrial pressure was normal in every instance

An inverse correlation between the shunt and the para-amino-hippurate clearance was demonstrated If the shunt exceeded 30 % of the left ventricular output low figures for effective renal plasma flow were frequently observed There was no correlation between the pulmonary arterial pressure and the effective renal plasma flow

In most cases with a shunt larger than 30 % of the left ventricular output the renal fraction of the systemic blood flow was low before operation There appeared to be an inverse correlation between the shunt and the renal fraction of the systemic blood flow

The true endogenous creatinine clearance exceeded 100 ml/min/1 73 m of

body surface area in every instance thus being normal. No correlation between the cardiopulmonary hemodynamics and the creatinine clearance could be demonstrated.

Preoperatively a high filtration fraction was frequently observed in cases with pulmonary hypertension or with shunts exceeding 40 % of the left ventricular output. A positive correlation existed between the shunt through the ductus and the filtration fraction. There was also a slight correlation between the pulmonary arterial pressure and the renal filtration fraction.

Postoperatively the para-amino-hippurate clearance and the renal fraction of the peripheral blood flow increased in most of the cases. The high filtration fraction decreased on an average and the creatinine clearance remained unchanged. Thus, the renal circulation became entirely normal in the children with a normal pulmonary arterial pressure. In the group which before operation had pulmonary hypertension, the effective renal plasma flow and the renal fraction of the systemic blood flow remained at the lower limits of normal, and the filtration fraction was on an average still slightly above normal even postoperatively. However the last postoperative investigation showed in three of these cases recanalization of the ductus.

A high filtration fraction is necessarily not a sign of renal vascular disease. Increased tone in the efferent glomerular arterioles seems to be of importance in maintaining a normal glomerular filtration rate in children with patent ductus arteriosus despite decreased blood supply to the kidneys.

Hypothermia and Transfusion with Oxygenated Blood in the Treatment of Asphyxia Neonatorum

by BJÖRN WESTIN
RUNE NYBERG, JAMES A. MILLER, JR. and ERIK WEDENBERG

(Supplement 139)

The rationales for the use of hypothermia and transfusions with oxygenated blood in *neonatal* asphyxia are presented, and their techniques are described.

Clinical trial in ten cases of *severe neonatal* asphyxia is reported. An evaluation of the condition of the infants was made with serial *Apgar* scorings at birth, before and after cooling and before and after blood transfusions. All infants showed such a pronounced improvement in association with the treatment that it seems justified to postulate an interrelationship. The possible physiological background is discussed. Apneic periods ranged from 8 to 79 minutes. Infants started breathing even at body

temperatures of 23 C The slopes of the cooling curves, as determined by rectal temperatures, were evaluated and estimations were made of the circulatory component of the cooling curve Changes in respiratory and heart rates electrocardiograms and blood pressure during rewarming in the temperature range 23 –37 C were described One infant died at an age of 30 hours in respiratory distress The autopsy showed hyaline membranes with atelectasis

Physical examination of the nine surviving infants and their growth, motor and speech developments showed no deviations from normal. Hearing tests, encephalograms and development tests, performed repeatedly were within normal ranges.

Experience with a limited number of cases has been reported extensively as an introduction to new resuscitative methods. The methods have subsequently been employed in additional cases, both by us and by others, with results similar to those reported here

Acta Paediatrica 51 7??—720 Nov 196

PROCEEDINGS OF PEDIATRIC SOCIETIES

Finnish Paediatric Society

Meeting September 8 1961

A. *Chorimus*, Athens. Infantile pyknocytosis. (T be published lsewhere)

R. E. *Bonham-Carter* and *D. Waterston* London. Surgical results of children under the age of one yea w th congenital mal formations of the heart.

Meeting October 21 1961

Round Table Discussion on Health Supervision of Teenagers.

Participants O. Wasz-Höckert (Moderator), Lecturer in Paediatrics, University of Helsinki,

H. Hortling, Lecturer in Internal Medicine University of Helsinki, Consultant of the Teenage Unit, Folkhälsan,

S. Landtman Chief Medical Officer Helsinki City Elementary Schools,

M. Palonheimo, Psychiatrist Consultant of the University of Helsinki Student Health Service

E. Petrakey Ph. D. Member of the National Board of Education, and

O. Widholm, Lecturer in Gynecology and Obstetrics, University of Helsinki, Consultant of the Teenage Unit Folkhälsan

O. Wasz-Höckert Child W lfare Centers these days are very efficient—the infant mortality in Finland last year as less than 2 ,—and children are medically supervised up t the school-age of 7 when the school medical officer takes over. This supervision continues in public schools till the age of 15 but the great majority of those who, at the age of 11 years, are accepted for study in grammar schools are still without regular supervision by ph sician or nurse. In this coun ry only relatively few grammar school ha had school medical officers and nurses mainly in Helsinki, where private organisation (Samfundet Folkhälsan) also has run a teenage unit for two years. As the government and the Mannerheim League are bout to take countrywide action in this important field the Society has invited some experts to discuss the question

H. Hortling: The hormonal dev lopment during adolescence concerns—as is well known—mainly growth and the sexual maturing. As a rule youngsters of the same age are in the same stage of development. However with the aid of simple new tools, as for instance the determination of the hormonally regulated bone age according t the tlas of Greulich & Pyle it has been shown that deviations from normal development are relatively frequent. Such disturbed maturation manifests itself not only in b-normal height or sexual maturation. An adolescent with abnormal bone age seems t have more difficulty in get ing along ith his coevals than normally developed ones and he often behaves differently. Abnormal physical development may also be on ributing factor to the genesis of man roubles and complaints. It seems that mere larification of the causes for the di ergen ex ernal shape is of help t the young boy or girl concerned. Sometimes hormone therapy ma be indicated. It is now possible guide hormonal treatment by simple means and thus avoid side-effects.

Endocrinological as well as p chiatric

considerations were the main ones in starting an out patient teenage clinic at the Samfundet Folkhälsan institution in Helsinki. At this clinic a general practitioner a specialist in internal medicine an endocrinologist, a psychiatrist, a gynecologist, a psychologist and a nurse are working jointly The patients are examined not only from a general clinical point of view but also with regard to the hormonal state and the sex chromatin pattern Some psychological and intelligence-tests are also made The results are promising

With regard to medical care in schools it seems important to perform a routine examination of all pupils, and especially of those in whom sudden changes in behaviour or ability are observed.

S. Lahdensuu It is essential for effective health supervision in schools that it can be done in adequate premises in each school. The medical officer and the school nurse must have at their disposal a room which is so located that noise from the playground, practising choirs, workshops or other normal school activities does not disturb them. Auscultation and hearing examinations require quiet surroundings. We find that 4–5% of our pupils have defective hearing, and about 8–10% need the services of an ophthalmologist Proper care of vision and hearing is important for good progress in learning

As physical health has improved rapidly mental health aspects have gained in importance These are now our main concern in school health There is a good opportunity at this age for promoting mental health. Unfortunately a rivalling dualism seems to exist in this sphere: psychologists and teachers versus psychiatrists and medical officers. Success can be achieved only through balanced and properly divided teamwork.

M. Palohelmo First some general remarks. We are speaking about health services and not about the treatment of sick children. These two are often confused. It is easier to find out the ills which cause illness than to discover which factors, through their absence cause disease In the field of mental health work this is still more difficult I should like to define mental health as a possibility to a rich human life" The goal of school mental health activities should thus be to create such an atmosphere in the school that it can help the children to grow and mature in a way which will lead to a rich form of human living Teenage youngsters are still often very much dependent on their parents and this dependence should always be taken into consideration when dealing with health problems of youths.

There are three different forms of mental health work in schools, mental health education proper atmosphere therapy and various forms of individual treatment. Mental health education is a rather difficult job, but it can be done. Traditional academic psychology does not help here very much; the emphasis must lie on interpersonal relations and understanding of human motivation and reactions. One could easily outline a text book on this subject. There are two special questions which should be particularly dealt with, sex education and education of young girls towards motherhood. Teachers are not always apt to do this kind of work. The teachers of gymnastics could be entrusted with this work, but their education then should necessarily be broadened considerably

Atmosphere therapy aims at an atmosphere of free expression and absence of fear and tension in school life Much can be achieved with group work. Teachers should have group counselling meetings in order to support their endeavours in this direction. Teachers themselves have often rather difficult emotional problems.

A clinic for teenage youngsters is evidently needed. One has to bear in mind that clinical work is the doctors prerogative and has to be separated from health education; the doctors are often poor teachers. Psychiatric consultation is often needed, therefore a well trained psychiatrist should be available Moral and spiritual values have often a very significant meaning for young people and should not be forgotten. All doctors are not well versed in this field and tend to neglect their value.

E. Pentkanen: I give my full support t

ary measures to promote the health supervision of teenagers. In practice this boils down to the question of such a system as makes possible a continued contact with the pupils. One would think here of the teachers of physical education, seconded by a school puberty fall into a category not usually covered by either pediatricians or gynecologists. The average age of girls in puberty has clearly fallen in the last few decades; this is reflected, for example, in the age for menarche which now is about 1..8 years in Finland. It can also be stated that this age limit is slightly lower for town girls than for girls from rural areas. If the menarche occurs too soon, before the age of 10–11 years, or too late after the age of 17 or possibly even 16, some kind of a developmental disorder exists. A congenital anomaly or endocrine dysfunction may be present.

For the examination of disorders of this kind a special out-patients clinic, with adequate facilities, is absolutely necessary. Above all, it should be clearly emphasized that patients of this age require extremely tactful treatment, since for the first time in their lives, they are encountering gynecological problems. It must also be borne in mind that the examination of young girls requires special equipment, e.g. for vaginal inspection, and that local anesthesia must not be forgotten since the hymenal region in children is very sensitive. For an assessment of the endocrine condition clinical tests must be used in addition to the evaluation of the external phenomena of sexual development. Such tests include the bone age PBI and the Papanicolaou test, the last being particularly valuable in the determination both of the degree of purity and of the estrogen and progesterone balances. If an inflammatory condition is examined, a pH determination and bacterial cultures should also be employed.

Detailed information about the conditions in the patient home are of very great importance they are often reflected in menstrual disorders. The mother plays very great part in the child attitude towards gynecological questions, but during a routine consultation social problems are not usually revealed without the help of an out patient clinic run on teamwork principles. The high cost of an examination may also prove a deterrent factor and for this reason I believe that our Teenage Out-patient Clinic has nurse. The professional training of physical education teachers should however be modernized, with more emphasis on health education than anatomy and other subjects of a more or less medical character.

Attention should be drawn to the working conditions in schools. To quote one basic example I should like t mention the highly defective ventilation of our class-rooms. In spite of modern "automatic pressure ventilation mechanisms the classrooms stink, and this has an immediate effect on the pupils mental efficiency.

On the whole the organization of the entire school life displays many features which continue to be maintained mainly by force of tradition. W should seriously go int this, and ask oursel es whether the daily classes really should start at 8 a.m., or whether the annual holidays are of appropriat length and t proper dates. I it indeed, right and proper to let the school year come to a close at the end of May? Should we not rather consider the possibility of placing this important event t some other time, which would then lea e the long vacation over the summer months free from any supplementary work and put an end to the existing system of conditional moving up. Moreover has everything been done t make the youngsters make health and really worthwhile use of their summer vacation? At present, the better part of t devoted to work in arious forms in order t earn ample pocket money which, again, is seldom wisely used.

And most important of all, the ment l atmosphere of the class-room should be li berated from the manifold fears, apprehensions and anxieties which now seem t place a highly undesirable burden on the pupils minds and thus directly influence their mental health and capacity for work. I is here that the co-operation of school psychiatrist is of urgent need.

O WIDHOLM: It may seem strange that a child should need a gynecologist, but it has emerged from this discussion that the gynecological troubles of girls at the age of attracted a large number of patients who would otherwise never have been examined, since they lacked the money

From my experience I am strongly convinced of the need *for a special out patients* clinic of this type. It supports the school doctor s strenuous routine efforts and is likely to disclose pathological conditions at an early age while therapeutical measures may still be found.

O WALZ-HÖCKERT: The discussion of the panel, given here only very briefly clearly showes the urgent need of proper health supervision of teenagers. This should be organized, especially for secondary school pupils, but naturally also for those who have finished primary school by the age of 15 and continue with some practical education.

A school medical officer alone is not enough to carry out efficient health supervision of teenagers; to this end a school nurse *is needed in addition. Together they should* try to influence and enlist the cooperation of the teachers in order to create a healthy mental climate at school. The need for consultations by psychiatrists, gynecologists and endocrinologists was emphasized. In larger cities these should be available in a special adolescent clinic.

Meeting December 9 1961

P Halonen A measles vaccine and an adsorbed pol myelitis-DTP vaccine study Published in *Acta Pædiat* (*Stockh*) *51* 401 and 409 1962

DISCUSSION

O WALZ-HÖCKERT: It will be very interesting to learn for how long the measles-vaccinated children will have a demonstrable amount of antibodies. The most obvious practical value of a measles vaccine is in providing the possibility of protecting children, in whom getting measles is regarded as involving a special risk. — P FORSSELL: The use of a "Salk type" measles vaccine increases the chances of contracting the disease in adult life, with increased frequency of complications.

L. Hjelt Praenatal infections

Different routes of infection as well as their respective manifestations in different organs were discussed. The importance of a careful clinical examination and close observation of the child in addition to studies of the umbilical cord, the placenta and the bacteriology were emphasized as, here too, a correct diagnosis is a prerequisit for successful therapy

N Hallman Paediatrics in Australia and New Zealand. Report of a journey made in April–May 1961

Annual Meeting February 17 196*

N Hallman The need for and distribution of paediatricians in th country

Ilmari K ntero Helsink

BOOK REVIEW

William A Silverman. Dunham Premature Infants (Third Edition)

Paul B Hoeber Inc., Medical Division of Harper & Brothers. New York, N Y 1961 5?2 pp.

Doctor Silverman has extended the classical" Dunham to some 460 pages of very readable material. The book is, like its predecessors, devoted to various problems associated with immaturity The author has succeeded in presenting a many-faceted view of one of the major fields of modern pediatrics His revision is clear and concerns all the more practical questions in regard to the immature infant. The rather voluminous bibliography given at the end of each chapter is commendably international and well selected and quotes important investigations of the past as well as recent research and experience.

The advancement of our knowledge regarding prevention and care of immaturity although a major target of present pediatric research, is still only at its beginnings. So many questions in this field remain unanswered that we often have t depend a great deal on personal experience. For this reason the opinions given by the author at the end of the various paragraphs on therapy and prevention are valuable and are certainly t be recommended as instructions based on our present-day knowledge regarding the management of immaturity

Silverman Dunham is an excellent guide for any doctor in charge of the care of immature infants but is also an easily read, complet textbook for the student who wants to know more about various aspects in this particular field. It is unfortunate that the publishers have chosen t put such an unappealing cover on such an ppealing book.

Göran Wallgren, Stockholm

Lars Hagbard Pregnancy and Diabetes Mellitus. Ch. C. Thomas, Springfield, Illinois, U.S.A.

In the American Lecture Series a new volume has appeared belonging to the section Gynecology and Obstetrics Pregnancy and Diabetes Mellitus" by Lars Hagbard, who is associate professor of obstetrics t the University of Gothenburg Sweden. His study is based upon experiences from 534 diabetic pregnancies observed during the years 1948–1960 Only pregnancies which proceeded beyond the 28th week or resulted in the birth of a child weighing at least 1000 g were considered. All deliveries occurred in hospitals. Of pediatric interest is the fat of the infants of the diabetic mothers. The perinatal mortality was 10%, in the best supervised group (~4 times higher than in the standard population). The causes of the high mortality are the high incidence of malformations, the oversize and edematous state of the infant and morphological and functional disorders in the internal organs (fetopathia diabetica"), which may exist also as a prediabetic condition. Malformations occurred in in the best supervised (during the 1st trimester) diabetic mothers infants increasing t roughly 6% in the other diabetic women (1 in standard population) The malformations are due to some obscure damage during the first trimester of embryonic lif There no correlation between the rat of malformation and the duration and severit and the age at onset of the disease Respira in distress was the most common disorder in the newborns and was associated b high mortality Many of the bnormalities found in the infants are connected with best immaturity In addition to this the infants hav lower vitality than other infants of the same gestational age. The uthor stresses that there is something injurious in

trauterine environment in diabetic pregnancies that makes it difficult for the fetus to adapt itself to extrauterine life. The author discusses the following causes: hypoglycemia, fetal acidosis, electrolyte disorders, hyaline membranes and hypocalcemia. The most effective way to diminish the risk of perinatal death of the infants is to deliver the mothers as late as possible. Satisfactory medical and obstetrical antepartum care makes it possible to lengthen the duration of pregnancy. Apart from the increased morbidity and death rate during the first year of life, the prognosis for children of diabetic mothers does not differ from that of other children, except as regards their inclination to acquire diabetes.

Parenterale Ernährung

Nutritio et Dieta, Supplementum ad Vol. 3 (1961), 136 pp.

Increasing interest in nutritional research during recent years has led to the founding of several new journals. One of these is *Nutritio et Dieta*. This periodical organized in Basel a symposium on parenteral fluids, under the chairmanship of Prof A. Hottinger October 1–2, 1960, in connection with the university 500th anniversary. The book contains ten introductory talks, by authors from Switzerland, France, Sweden, Germany and Austria. As was expected, the paper on intravenous fat emulsions (B. Edgren) aroused particular interest. However, the quality of the contributions is uneven. Some are verbose without containing anything essentially new and it would have been helpful if they had all had summaries and references. The discussions are collected in a special section at the end, with a useful detailed reference list. The technical notes on the last page are elementary but no doubt intended for the less initiated reader.

Bo Vahlquist, Uppsala

Peele, Talmage L.: The Neuroanatomic Basis for Clinical Neurology

2nd ed. 662 pp. McGraw Hill, London, 1961. Price £6 4s.

The second edition of Dr Peele's exhaustive monograph on the structure of the central nervous system correlated to its function retains the basic pattern of the 1954 edition. New material has been woven into the text. New electron microscopy data have been added to the chapters dealing with nerve cells, fibers and glia, for example the finding that myelin sheaths are derivatives of the Schwann cell cytoplasm. This important observation will probably open up an experimental approach to the study of the abnormal metabolism of myelin in cerebral lipidoses and demyelinization disorders. No electron micrographs are included, however. A compilation of such pictures from the scattered EM-studies in the literature would certainly have raised the value of the monograph considerably. Some 350 photographs, drawings and diagrams are presented, of which some are new. They are all in black and white, and in many instances multicolored drawings would have added clarity to the topography of vasculature pathways and nuclei. A new atlas of brain stem sections encompassing 52 different levels is very valuable; the reviewer would have liked a reference to the structures illustrated in these in the index, which is otherwise quite detailed. The extensive bibliography is almost doubled, now containing 1 633 references.

Despite the critical comments cited above, Dr Peele's monograph remains a very valuable book of reference to neurologists, pathologists and neuropathologists.

Björn I. Ivemark, Stockholm